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Systematic review and meta-analysis of the association of infection with *Toxocara canis* with atopy and asthma

Revisión sistemática y metaanálisis de la asociación de la infección por *Toxocara canis* con atopia y asma

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Abstract

The human toxocariasis is the most important cosmopolite helminth infection in the world. The infection can modulate the immune response of the infected paratenic host, and it is suggested that it is an important risk factor for the development of asthma and be associated with increased levels of different markers of atopy. The aim of this study was to conduct a systematic review and meta-analysis of the association between human toxocariasis with asthma and atopic diseases. The literature search identified 1705 papers on the association of *Toxocara* spp with asthma, Then, 24 papers were selected based on the inclusion and exclusion criteria, following the PRISMA protocols. These papers served to analyze association data as a risk factor for increased asthma and investigate

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the association of this infection with the appearance of atopy markers (specific IgE). The results did not indicate association between asthma and *Toxocara* spp seropositivity, although there was a positive trend (OR 1.47; 95% CI 0.92-2.33). However, when studies were classified by type a positive association in the case-control type studies was found (OR 1.69; 95% CI 1.06-2.70). Furthermore, there was a positive association with this atopic marker in the analysis of the association of toxocariasis with specific IgE (OR 1.77; 95% CI 1.19-2.64). The evidence found was not entirely conclusive regarding the possibility of having *T. canis* infection as a risk factor for the development of asthma, although there is a positive statistical trend. On the other hand, the association with specific IgE results supports previous findings in the literature, where helminth infections can stimulate the production of this type of antibody, leading to a positive association with atopy.

Key words: helminth, public health, zoonosis

Resumen

La toxocariasis humana es la helmintiasis cosmopolita más importante del mundo. La infección puede modular la respuesta inmune del huésped paraténico infectado, y se sugiere que es un factor de riesgo importante para el desarrollo de asma y estar asociado con niveles elevados de diferentes marcadores de atopia. El objetivo de este estudio fue realizar una revisión sistemática y un metanálisis de la asociación entre la toxocariasis humana con asma y enfermedades atópicas. La búsqueda bibliográfica identificó 1705 artículos sobre la asociación de *Toxocara* spp con asma. Luego, se seleccionaron 24 artículos con base en los criterios de inclusión y exclusión, siguiendo los protocolos PRISMA. Estos trabajos sirvieron para analizar datos de asociación como factor de riesgo de aumento del asma e investigar la asociación de esta infección con la aparición de marcadores de atopia (IgE específica). Los resultados no indicaron asociación entre asma y seropositividad a *Toxocara* spp, aunque hubo una tendencia positiva (OR 1,47; IC 95% 0.92-2.33). Sin embargo, cuando los estudios se clasificaron por tipo se encontró una asociación positiva en los estudios de tipo caso-control (OR 1,69; IC 95% 1.06-2.70). Además, hubo una asociación positiva con este marcador atópico en el análisis de la asociación de la toxocariasis con la IgE específica (OR 1.77; IC 95% 1.19-2.64). La evidencia encontrada no fue del todo concluyente respecto a la posibilidad de tener infección por *T. canis* como factor de riesgo para el desarrollo de asma, aunque existe una tendencia estadística positiva. Por otro lado, la asociación con resultados de IgE específica respalda hallazgos previos en la literatura, donde las infecciones por helmintos pueden estimular la producción de este tipo de anticuerpos, lo que lleva a una asociación positiva con la atopia.

Palabras clave: helminto, salud pública, zoonosis

Introduction

The recently updated Old Friends Hypothesis, an evolution of the hygiene hypothesis aligning with Darwinian medical principles and supported by contemporary epidemiological and experimental findings (Strachan, 1989; Maizels *et al*., 2014; Zhu et al., 2022; Rook, 2023), posits that the advent of modern urbanization characterized by concrete and asphalt since the early 19th century has led to a gradual rise in immunoregulatory disorders (Blackley, 1991; Maizels *et al*., 2014). This increase is believed to stem from the urban setting's diminished exposure to microorganisms that have historically co-evolved with mammals (Maizels *et al*., 2014; Pontes-de-Carvalho & Mengel, 2014; Rook, 2023). These organisms played a pivotal role, as shaped by co-evolutionary pressures, in establishing baseline levels of immune regulation, furthermore, different studies have tried to understand the relationship between parasitic infections and allergic diseases (Shirakawa *et al*., 1997; Bodner *et al*., 1998; von Mutius *et al*., 1999; Matricardi & Bonini, 2000; Arrais *et al*., 2020, 2022; Cooper *et al*., 2021). In this sense, helminth infections have been the main objective of these studies and have shown controversial results (Cooper *et al*., 2003; Cooper, 2009; Feary et al., 2011; Alcantara-Neves *et al*., 2012). For example, intestinal helminths such as *Trichuris trichiura,* although in general, has been described as protector factor of atopy (Alcântara-Neves *et al*., 2014; Rodrigues *et al*., 2008), it has shown a positive association with the development of atopic asthma in children under four years of age (Alcântara-neves *et al*., 2010).

Following this line of studies, one of the parasites of great interest is *Toxocara* spp, a roundworm of dogs (*Toxocara canis*) and cats (*Toxocara cati*) (Bowman, 2020; Dantas-Torres *et al*., 2020). *T. canis* is the principal agent of human toxocariasis, followed by *T. cati.* (Bowman, 2020). This is one of humans' most prevalent zoonotic helminth infections (Alcântara-Neves *et al*., 2010). Children are the most vulnerable to this infection due to hygiene habits and playing with pets (Kroten *et al*., 2018). The human disease leads to the development of clinical manifestations termed visceral larva migrans syndrome, ocular larva migrans, neurotoxocariasis, and covert toxocariasis (or asymptomatic) (Magnaval *et al*., 2001; Walsh & Haseeb, 2012). Furthermore, the asymptomatic form has been associated with low cognition (Walsh & Haseeb, 2012), and like most helminthic infection inadequate immune response to vaccination (Cooper *et al*., 2001).

Infection by *Toxocara* spp is associated as a risk factor in the development of asthma (Cooper, 2008; Fialho *et al*., 2018). Studies have shown that, in addition to children, another vulnerable group comprises individuals with daily contact with dogs at home or work (Agudelo *et al*., 1990; Aguiar-Santos *et al*., 2004; Buijs *et al*., 1997; Habluetzel *et al*., 2003; Mendonça *et al*., 2012; Kanobana *et al*., 2013; Merigueti *et al*., 2022; Mubarak *et al*., 2023; Nijsse *et al*., 2014). Infection by *Toxocara* spp was first associated with the development of asthma by Desowitz *et al.* (1981), when it was shown that the prevalence of toxocariasis was 3.67 and 1.28% in asthmatic and non-asthmatic children, respectively ($p<0.01$).

The findings of *Toxocara* spp as a risk factor for the development of asthma have been controversial. Some studies has reported a positive association between this infection with asthma symptoms (Agudelo *et al*., 1990; Buijs *et al*., 1997; Fernando *et al*., 2009; Kanobana *et al*., 2013); however, other studies did not find a statistically significant association between infection and the development of asthma (Sharghi *et al.*, 2001; Muñoz-Guzmán *et al*., 2010; Mendonça *et al*., 2012). In this sense, a study conducted in Brazil by Alcântara-Neves (2014) showed a positive association and dose-response between anti-*Toxocara* IgG seropositivity and total IgE levels, showing that the presence of the parasite is influencing the stimulation of IgE production. To date, two meta-analyses have been published on *Toxocara* spp association of infection with asthma. However, there is still no systematic review or meta-analysis on the association between *Toxocara* spp infection and markers of atopy (Li *et al*., 2014; Aghaei *et al*., 2018).

The present work aims to update the data on the relationship between *Toxocara* infection and asthma, as well as to describe the findings between this infection and atopy throughout a systematic review and meta-analyses study to better understand the contradictory results of this association.

Material and Methods

This systematic review and meta-analysis followed the PRISMA protocols for these studies (Page *et al*., 2021).

Search Strategy

The search for information was based on four scientific platforms NCBI (PubMed, http://www.ncbi.nlm.nih.gov/pubmed/), Elsevier Group (Science Direct, http://www.sciencedirect.com/), Scientific Electronic Library Online (SciELO, http://www.scielo.org/php/index.php?lang=es), and Scholar Google (Scholar Google, https://scholar.google.com/). Two investigators selected papers written in English, Portuguese, and Spanish. The keywords used for identifying the potential articles were: *asthma*, *allergic disease*, *atopic asthma*, *wheeze*, *wheezing*, *airway hyperreactivity*, *inflammatory airway response*, *Toxocara*, *Toxocara canis*, *Toxocara* spp, *Toxocariasis*, *Toxocara infection.*

Inclusion and Exclusion Criteria

The criteria of inclusion were: 1. Population (>50); 2. Identification of gender of the study population; 3. Identification of the age of individuals in the study population; 4. Percentage of prevalence or incidence of *Toxocara* spp infection in the study population, 5. Rate of asthma in the people; 6. Percentage of *Toxocara* spp seropositive in the populations; 7. Type of study used (transversal, case-control, prospective). Other papers were excluded.

The interaction between *Toxocara* spp infection and atopy in the selected papers were analyzed, and those with information related to atopy markers were identified. The markers for the determination of atopy reported in the literature are the skin prick test (SPT) and the dosage of specific IgE. However, within the studies selected in this meta-analysis, only the studies by Mendonça *et al*. (2013) and Gonzalez-Quintela *et al*. (2006) use both markers of atopy, while the works of Buijs *et al.* (1994), Silva *et al.* (2017), and Momen *et al.* (2018) only used specific IgE.

Data Extraction

Data were extracted from articles that met the inclusion and exclusion criteria. The extraction was performed globally and the data were subsequently grouped according to the type of study and atopy markers. In addition, the number of seropositive and seronegative cases for *Toxocara* spp, the number of asthmatic cases and the number of seronegative cases for *Toxocara* spp, non-asthmatic cases seropositive for *Toxocara* spp IgG and atopy markers were recorded. Finally, no discrimination was made by age groups within the analyzes carried out.

Statistical Analysis

Binary logistic analysis was performed using the Odds ratio (OR) with a 95% confidence interval (95% CI) to report the results of the association between *Toxocara canis* infection and asthma development and atopic disease. The heterogeneity of the 25 studies included in the analysis indicated that the homogeneity hypothesis could not be accepted, and the random-effects model was used to calculate the total OR. In addition, a funnel analysis was performed to analyze possible bias in the analyses of the selected studies. All analyses were performed using the NCSS Statistical Software 2019.

Results

Search for Scientific Studies

It was possible to identify 1705 papers on the association of *Toxocara* spp with asthma, in which one or a combination of used keywords appeared in the titles or abstracts. These abstracts were evaluated according to

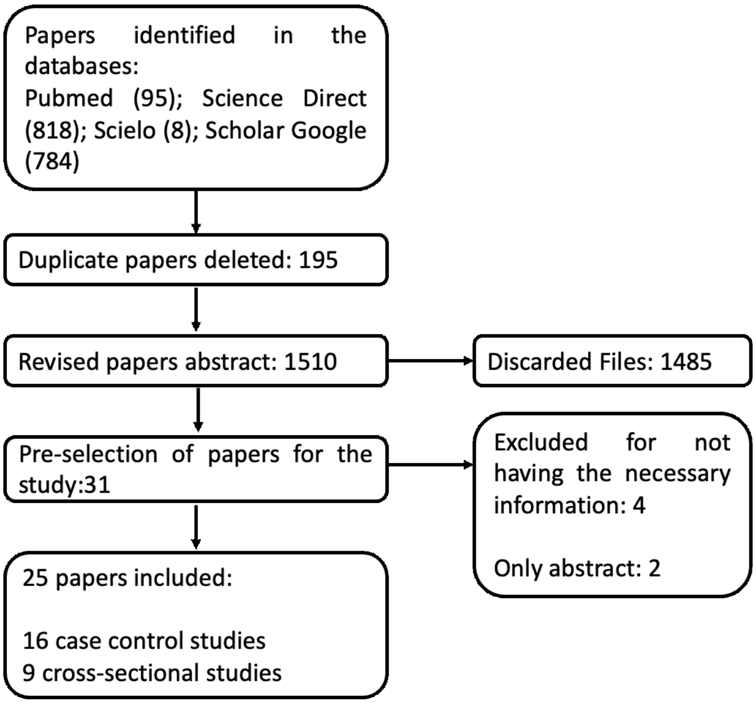

Figure 1. Papers searched and selection of studies in the meta-analysis through PRISMA Protocols on the association of toxocariasis with asthma

the inclusion and exclusion criteria and therefore, 31 articles were selected. Subsequently, in the second stage of evaluation six articles were discarded, 5 for not having all the required information in their methodology, and 2 for being only summaries. Based on those 24 papers met the inclusion criteria, being 9 cross-sectional and 16 case-control studies. These studies were published between 1981 and 2022 (Figure 1).

In addition, in these papers was searched data on atopy markers, such as IgE and SPT tests, and as a result five 5 papers were identified for both markers and two with SPT data.

Selected Studies

In all studies that were part of this research 4909 individuals were included that is, the populations of the 24 selected studies, of which 2440 were diagnosed as seropositive for *Toxocara* spp (49.70%) and 2450 individuals were considered asthmatics (49.90%). Among the latter individuals, 800 were in turn positive for *Toxocara* spp, representing 32.65% of this group.

Of the 24 studies that are part of this meta-analysis, 11 focused on evaluating the association of *Toxocara* spp seropositivity with asthma in adult patients, one of them had a mixed population among children, young, and adults, and 12 studied children's populations. The study population consisted of individuals from Brazil, Cuba, China, Egypt, Indonesia, Mexico, The Netherlands, Peru, Sri Lanka, Turkey and the United States of America.

The data of this study were also extracted to determine the possible association between *T. canis* infection and markers of

Table 1. Results of studies included in an analysis of the relationship between asthma and toxocariasis in humans

Cod.	Study	Asthma cases	*Toxocara* seropositive with asthma	Healthy controls	*Toxocara* seropositive without asthma	OR (95% CI)
1	Buijs *et al.* (1994)	73	10 (13.69%)	639	42 (6.57%)	2.32 (1.12 – 4.79)
2	Buijs *et al.* (1997)	94	17 (18.08%)	1285	97 (7.54%)	2.75 (1.57 – 4.81)
3	Cadore *et al* (2016)	156	20 (12.82%)	52	4 (7.70%)	1.61 (0.55 – 4.72)
4	Chan *et al.* (2001)	80	14 (17.50%)	58	5 (8.62%)	2.68 (0.93 – 7.69)
5	Cobzaru *et al* (2012)	76	20 (26.31%)	88	4 (4.54%)	6.81 (2.32 – 19.95)
6	Desowitz *et al.* (1981)	80	1 (1.25%)	96	0 (0%)	3.64 (0.14 – 90.62)
7	Fernando *et al* (2009)	100	29 (29.00%)	96	10 (10.41%)	3.39 (1.57 – 7.34)
8	Ferreira *et al.* (2007)	50	23 (46.00%)	431	80 (18.56%)	3.73 (2.04 – 6.80
9	Figueiredo *et al.* (2005)	106	65 (61.32%)	102	49 (48.03%)	1.70 (0.98 – 2.95
10	Fragoso *et al.* (2011)	245	78 (31.83%)	202	124 (61.38%)	0.29 (0.20 – 0.43)
11	Kanobana *et al.* (2013)	314	140 (44.58%)	644	244 (37.88%)	1.31 (1.00 – 1.73)
12	Kartasamita *et al.* (1994)	224	14 (6.25 %)	45	10 (22.22 %)	0.23 (0.09 – 0.55)
13	Khozime *et al* (2019)	50	4 (8.00%)	50	12 (24.00%)	0.29 (0.09 – 0.94
14	Kuk *et al.* (2006)	53	7 (13.20%)	50	1 (2.00%)	5.32 (0.88 – 32.14)
15	Kustimur *et al.* (2007)	124	12 (9.67 %)	60	3 (5.00 %)	1.82 (0.53 – 6.22)
16	Lopez *et al.* (2010)	47	27 (57.44%)	53	28 (52.83%)	1.10 (0.50 – 2.40)
17	Mendonça *et al.* (2012)	258	131 (50.77%)	898	409 (45.54%)	1.13 (0.70 – 1.82)
18	Momen *et al.* (2018)	40	18 (36.00%)	46	10 (21.73%)	2.85 (1.13 – 7.18)
19	Mosayebi *et al* (2016)	110	2 (1.28%)	70	0 (0.00%)	3.24 (0.15 – 68.67)
20	Muñoz-Guzmán *et al.* (2010)	285	88 (30.87%)	152	30 (19.73%)	3.30 (2.03 – 5.37)
21	Sadri *et al* (2019)	92	1 (1.08%)	100	0 (0%)	3.25 (0.13 – 81.01)
22	Shahat *et al.* (2019)	72	16 (22.22%)	72	5 (6.90%)	3.58 (1.28 – 10.01)
23	Sharghi *et al.* (2001)	95	8 (8.42%)	229	25 (10.91%)	0.77 (0.34 – 1.76)
24	Silva *et al.* (2017)	83	55 (66.26%)	708	448 (63.27%)	1.21 (0.91 – 1.59)
	Average					1.47 (0.92– 2.33)[1]

[1] Binary logistic analysis was performed using Odds ratio (OR) with a 95% confidence interval (95%CI)

atopy, such as IgE production. Of the total population analyzed, it was observed that 1270 individuals presented high levels of total IgE and of which 457 showed high levels of specific IgE for *T. canis* which represents 36% of the total of individuals who had high levels of specific IgE. On the other hand, the non-atopic population was 1799, of which 519 (28.84%) were positive for *Toxocara* spp infection. Besides, of the 25 studies, two showed data on SPT; for this, 1611 individuals were analyzed, of which 189 (11.73%) were SPT reactive and *Toxocara* spp seropositive.

Meta-analysis

Twenty-three studies analyzed the relationship between *Toxocara* spp infection and asthma (Table 1; Figure 1). The other study conducted by Gonzalez-Quintela *et al.* (2006) only evaluated the association between *Toxocara* spp and atopy. An OR of 1.47 (95%CI 0.92-2.33) was found, suggesting no association between asthma and *Toxocara* spp seropositivity. The results concerning the heterogeneity of the data and possible bias about the standard error are shown in Figure 3.

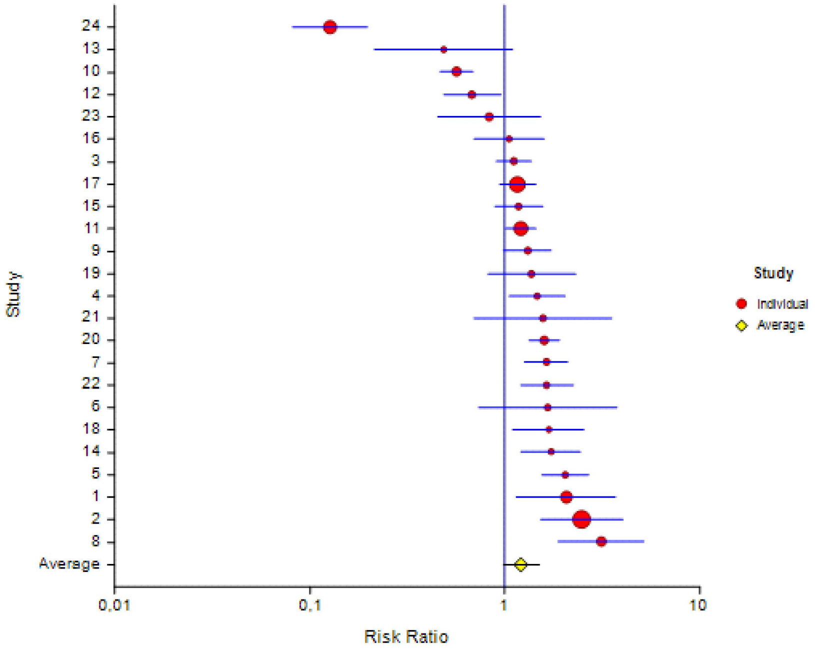

Figure 2. Analysis of the relationship between asthma and toxocariasis. Data of 24 studies. Odds ratio (red points) and 95% confidence interval (horizontal blue lines) are obtained from estimates of seropositivity for *Toxocara* spp among patients with asthma compared to controls (healthy individuals). The sizes of the squares represent the statistical significance of the studies included in the meta-analysis. The values corresponding to the testing random-effects model represent the final analysis of the meta-analysis (yellow point), and the horizontal bar represents the 95% CI (average). The ordinal numbers in the graph represent the order of entry of the studies in the statistical analysis reported in this manuscript.

When the types of studies were separated in the case-control studies, a positive association was observed between *T. canis* infection and asthma, OR 1.69 (95%CI 1.06-2.70) (Table 2; Figure 4). Figure 5 shows the result of the heterogeneity of this data evaluated.

On the other hand, the results of the analyses of the cross-sectional studies (Table 3), show no association between asthma and toxocariasis when taking data only from cross-sectional studies, OR 1.12 (95%CI 0.54-2.30). Table 4 and Figure 6 show the data on the possible association between parasitic infection by *Toxocara* spp and specific IgE production. In addition, heterogeneity was observed in the data of this analysis, OR 1.77 (95%CI 1.19-2.64). Meanwhile, of the 24 articles selected, only two evaluated the relationship between SPT and toxocariasis (18,45). In this sense, as shown in Table 5, the OR value was 1.04 (95%CI 0.49-2.17).

Discussion

Several researchers have investigated the impact of this disease on public health and how it can modulate the immune response of the human host, influencing the development of inflammatory diseases, allergies, autoimmune diseases, and an inadequate response to the vaccine (Cooper *et al*., 2001,

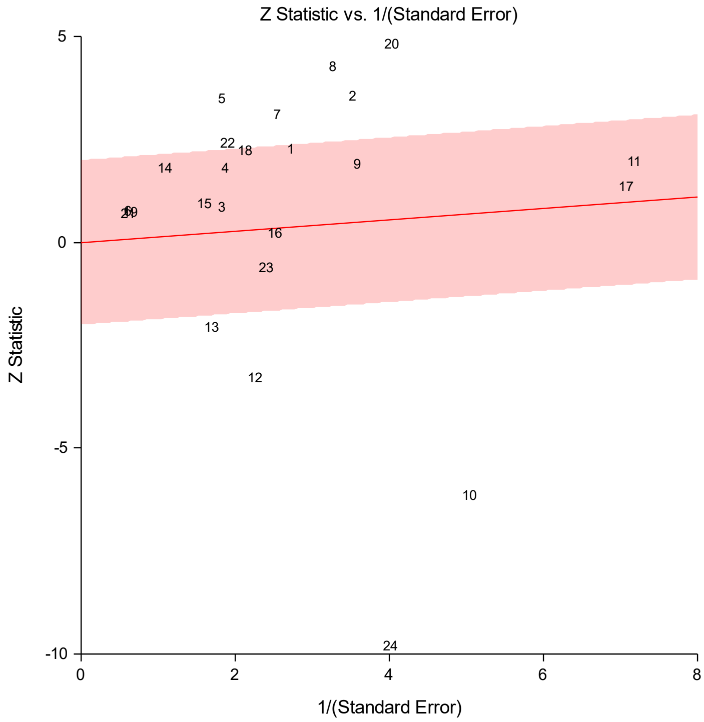

Figure 3. Heterogeneity of the data and the possible bias concerning the standard error of the 24 studies included in the meta-analysis. The ordinal numbers in the graph represent the order of entry of the studies in the statistical analysis reported in this manuscript. Publication bias using this Chi-square value tests the null hypothesis that all effects are zero versus the alternative that all studies had the same, non-zero effect.

2021; Bohnacker *et al*., 2020). Several studies have shown a wide difference between prevalence of *Toxocara* spp in several countries worldwide, being high in tropical areas, ranging from 7.3% in Colombia to 65% in Bahia, Brazil (Acero *et al*., 2001; Souza *et al*., 2011).

The present study did not show an association between *Toxocara* infection and asthma, although a trend towards a positive association was observed (OR 1.47, 95% CI 0.92-2.33). Thus, a lower prevalence of positive cases of asthma was observed in seropositive using information from 24 studies that met all the inclusion criteria regarding the association between *Toxocara* infection *vs* asthma. The results are consistent with the data already established in the literature on the effect of *T. canis* infection on asthma; however, the findings presented in this work are not consistently associated in cross-sectional studies (OR 1.12, CI 95% 0.54-2.30), but a positive trend is observed. In addition, these results may be more evident when the studies are separated by type, allowing this positive association to be kept in the analysis of case-control studies (OR 1.69, 95% CI 1.06-2.70).

Various studies that have focused on analyzing the risk factors for this infection have shown that maintaining contact with domestic animals such as dogs and cats poses a significant risk for developing *Toxocara* spp infection (Kostopoulou *et al*., 2017; Eslahi *et al*., 2020). Besides, the area of residence (urban or rural) represents a risk factor (Acero *et al*., 2001; Habluetzel *et al*., 2003).

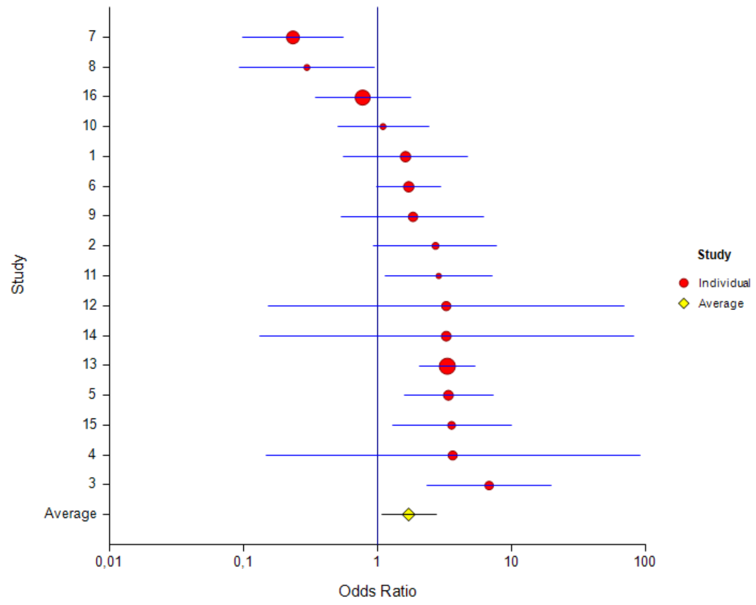

Figure 4. Case-control studies on the association between asthma and toxocariasis. Case-control Odds ratio (red points) and 95% confidence interval (95%CI, horizontal blue lines) are obtained from estimates of seropositivity for *T. canis* among patients with asthma compared to controls (Individual). The sizes of the squares represent the statistical significance of the studies included in the meta-analysis. The values corresponding to the testing random-effects model represent the final analysis of the meta-analysis (yellow point), and the horizontal bar represents the 95%CI (average). The numbers on the vertical axis represent the selected studies coded according to Table 2.

The interest on parasitic infection studies goes beyond *Toxocara* spp as other helminths have been recognized to show protective effects in other diseases caused by immunological disorders, such as the case of allergies (Rodrigues *et al*., 2008). However, Leonardi-Bee *et al* (2006) showed a small increase in the risk of asthma (OR 1.24, 95% CI 0.98-1.57) for people infected with helminth parasites. In addition, infection with *Ascaris lumbricoides* has been associated with an increased risk of asthma (OR 1.34, 95% CI 1.05-1.71) (Leonardi-Bee *et al*., 2006), whereas hookworm (*Ancylostoma duodenale necator americanus*) infection was associated with a reduction in the risk of asthma (Bohnacker *et al*., 2020; Cooper *et al*., 2021). However, studies on other parasites have shown interaction between parasitosis and immunomodulation. On this, Rodrigues *et al.* (2008) have demonstrated that *Trichuris trichiura* can be associated with the development of a protective response against type disorders allergic atopic, but depending of the parasitic load, stage of life in which the infection occurs, and time of infection.

The effects of one or more parasitic infections on the immune system should be considered, as shown by Alcantara-Neves *et al.* (2012) where co-infection by several types of helminths can cause immunomodulatory effects as followed by individual infections. Also, this group re-appraised the toxin hypothesis of allergy described by Palm *et al* (2012), proposing that the IgE-mediated hypersensitivity response evolved to counter

Table 2. Results of case-control studies on the association between asthma and toxocariasis in humans

Cod.	Study	Asthma cases	*Toxocara* seropositive with asthma	Healthy controls	*Toxocara* seropositive without asthma	OR (95%IC)
1	Cadore *et al.* (2016)	156	20 (12.82%)	52	4 (7.70%)	1.61 (0.55 – 4.72)
2	Chan *et al.* (2001)	80	14 (17.50%)	58	5 (8.62%)	2.12 (0.74 – 6.03)
3	Cobzaru *et al.* (2012)	76	20 (26.31%)	88	4 (4.54%)	6.81 (2.32 – 19.95)
4	Desowitz *et al.* (1981)	80	1 (1.25%)	96	0 (0.00%)	3.64 (0.14 – 90.62)
5	Fernando *et al.* (2009)	100	29 (29.00%)	96	10 (10.41%)	3.39 (1.57 – 7.34)
6	Figueiredo *et al.* (2005)	106	65 (61.32%)	102	49 (48.03%)	1.70 (0.98 – 2.95)
7	Kartasamita *et al.* (1994)	224	14 (6.25 %)	45	10 (22.22 %)	0.23 (0.09 – 0.55)
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9	Kustimur *et al.* (2007)	124	12 (9.67 %)	60	3 (5.00 %)	1.82 (0.53 – 6.22)
10	Lopez *et al.* (2010)	47	27 (57.44%)	53	28 (52.83%)	1.10 (0.50 – 2.40)
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[1] Binary logistic analysis was performed using Odds ratio (OR) with a 95% confidence interval (95% CI)

venoms and other toxic substances rather than macro-parasites. On the other hand, a kind of «*phylogenetic adaptative memory*» could be explained by cross-reactive Th2 immune responses by allergens sharing antigenic determinants with helminths in individuals who have not been in contact with those parasites (Pontes-de-Carvalho & Mengel, 2014).

However, although this evidence profiles different helminth infections as risk factors or in other cases as possible protective factors against allergic-type respiratory diseases, the infection by *Toxocara* spp is still not defined, because after decades of study the data from different investigations show inconclusive results, since some research shows as a risk factor (Buij*et al*., 1997; Pinelli *et al*., 2008; Kanobana *et al*., 2013), others have not shown any type of association (Sharghi *et al*., 2001; Kuk *et al*., 2006). Although the data displayed here is consistent with what has been widely observed in the literature on the possible association of *T. canis* infection with the development of asthma, it is crucial to indicate that the study by Mendonça *et al* (2012) is the first to show a statistically related negative relationship between *T. canis* infection and reactivity in SPT test.

This study also addressed the association of infection with increased IgE production in asthmatic individuals, however, the literature shows few studies in which the association between infection with *T. canis* and the development of asthma was studied (Buijs *et al*., 1997; Mendonça *et al*., 2013). This shows a significant gap in terms of understanding this type of relationship between illness and respiratory disease. It is somehow known that the presence of IgE is significant

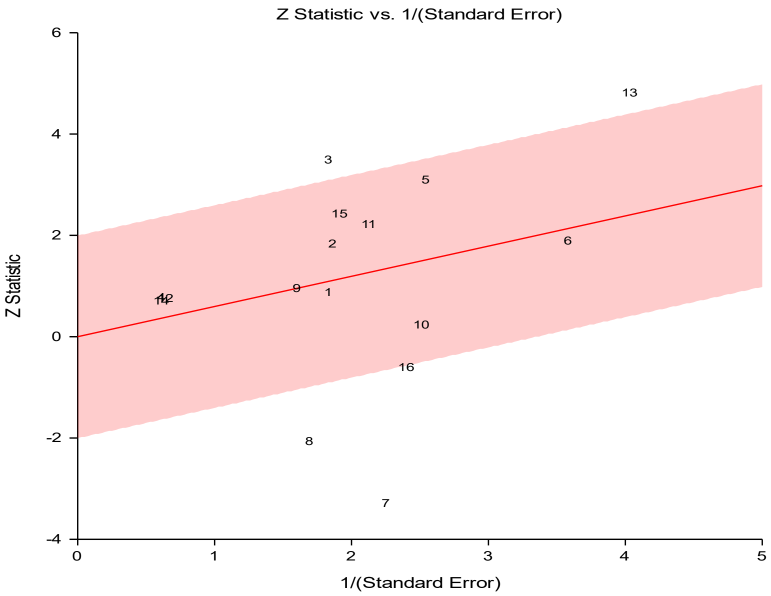

Figure 5. Heterogeneity of the data and the possible bias about the standard error of the Case-control studies. The numbers (1, 3, 5… 11, and 16) represent the selected studies coded according to Table 2. Publication bias using this Chi-square value tests the null hypothesis that all effects are zero versus the alternative that all studies had the same, non-zero effect.

Table 3. Results of cross-sectional studies on the association between asthma and toxocariasis

Cod	Study	Asthma cases	*Toxocara* seropositive with asthma	Non-Asthma	*Toxocara* seropositives non asthma	OR (95%CI)
1	Buijs *et al.* (1994)	73	10 (13.69%)	639	42 (6.57%)	2.32 (1.12 – 4.79)
2	Buijs *et al.* (1997)	94	17 (18.08%)	1285	97 (7.54%)	2.75 (1.57 – 4.81)
3	Ferreira *et al.* (2007)	50	23 (46.00%)	431	80 (18.56%)	3.73 (2.04 – 6.80)
4	Fragoso *et al.* (2011)	245	78 (31.83%)	202	124 (61.38%)	0.29 (0.20 – 0.43)
5	Kanobana *et al.* (2013)	314	140 (44.58%)	644	244 (37.88%)	1.31 (1.00 – 1.73)
6	Kuk *et al.* (2006)	53	7 (13.20%)	50	1 (2.00%)	5.32 (0.88 – 32.14)
7	Mendonça *et al.* (2012)	258	131 (50.77%)	898	409 (45.54%)	1.13 (0.70 – 1.82)
8	Silva *et al.* (2017)	83	55 (66.26%)	708	448 (63.27%)	1.21 (0.91 – 1.59)
	Average					1.12 (0.54– 2.30)[1]

[1] Binary logistic analysis was performed using Odds ratio (OR) with a 95% confidence interval (95% CI)

in the development of allergic diseases such as atopic asthma (Shamji *et al.*, 2021). Helminth infections usually produce IgE antibodies characterized by low levels of somatic mutation and very few signs of antigenic selection (Wang *et al.*, 2011; Wu *et al.*, 2017). On the contrary, the IgE antibodies in allergic populations display a high degree of somatic mutation and clear signs of antigenic selection (Kerzel *et al.*, 2010).

Table 4. Results of the studies on the association between IgE production and toxocariasis

Cod	Study	*Toxocara* seropositive	*Toxocara* seropositive/IgE ≥0.70kU/L	Non- *Toxocara* seropositive	Non- *Toxocara* seropositive/IgE ≥0.70kU/L	OR (95%CI)
1	Buijs *et a.l* (1997)	221	28 (12.66%)	1129	84 (7.44%)	1.96 (1.25 – 3.09)
2	Gonzales *et al.* (2006)	134	46 (34.32%)	329	70 (23.40%)	1.37 (0.90 – 2.09)
3	Mendonça *et al.* (2012)	557	288 (51.70%)	591	252 (42.63%)	1.24 (0.97 – 1.58)
4	Momen *et al.* (2018)	25	13 (52.00%)	15	5 (33.33%)	2.06 (0.56 – 7.46)
5	Silva *et al.* (2017)	333	82 (24.62%)	458	252 (55.02%)	2.84 (2.10 - 3.83)
	Average					1.77 (1.19 – 2.64) [1]

[1] Binary logistic analysis was performed using Odds ratio (OR) with a 95% confidence interval (95% CI)

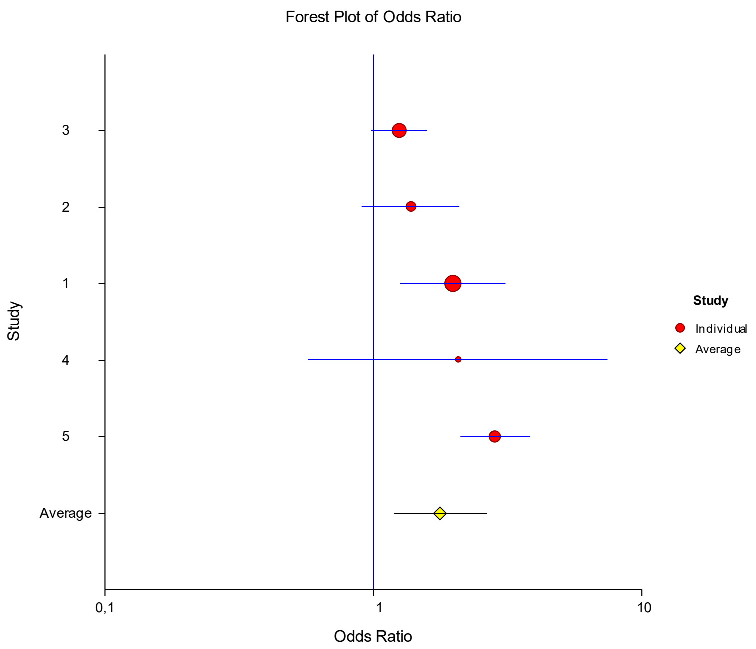

Figure 6. Studies on the association between IgE production and toxocariasis. Odds ratio (red points) and 95% confidence interval (95%CI, horizontal blue lines) of atopy data are obtained from estimates of seropositivity for *T. canis* among patients with atopy compared to controls (Individual). The sizes of the squares represent the statistical significance of the studies included in the meta-analysis. The values corresponding to the testing random-effects model represent the final analysis of the meta-analysis (yellow point), and the horizontal bar represents the 95%CI (Average). The numbers on the vertical axis represent the selected studies coded according to Table 4.

Table 5. Results of the studies on the association between reactive SPT and toxocariasis

Cod	Study	*Toxocara* seropositive	*Toxocara* seropositive/ SPT	Non-*Toxocara* seropositive	Non-*Toxocara* seropositive/SPT	OR (95%CI)
1	Gonzales *et al* (2006)	134	43 (32.08%)	329	77 (23.40%)	1.54 (0.99 – 2.40)
2	Mendonça *et al* (2012)	540	146 (27.03%)	608	205 (33.71%)	0.72 (0.56 – 0.93)
	Average					1.04 (0.49 – 2.17)*

*Binary logistic analysis was performed using Odds ratio (OR) with a 95% confidence interval (95%CI)

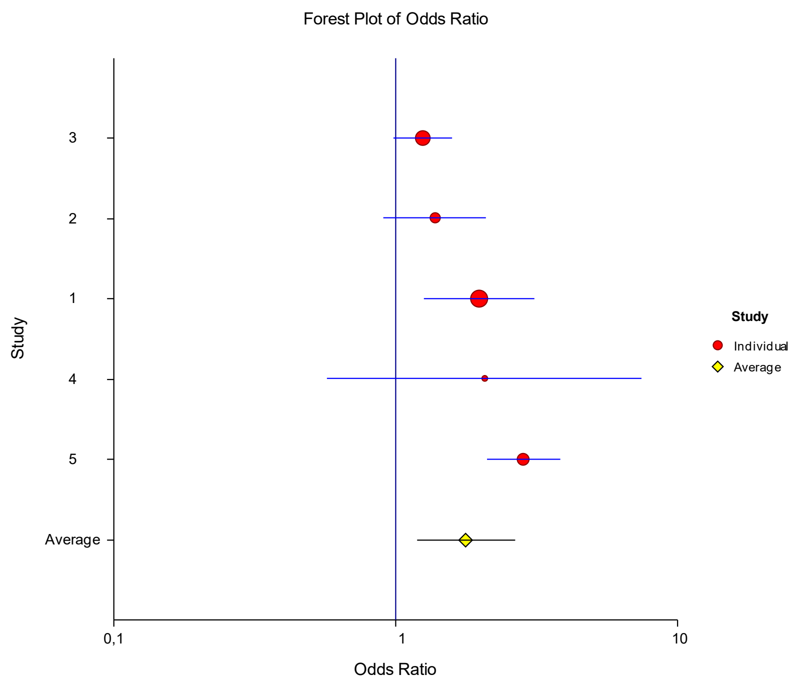

Figure 7. Studies on the association between reactive SPT and toxocariasis. Odds ratio (red points) and 95% confidence interval (95%CI, horizontal blue lines) of atopy data are obtained from estimates of seropositivity for *T. canis* among patients with atopy compared to controls (Individual). The sizes of the squares represent the statistical significance of the studies included in the meta-analysis. The values corresponding to the testing random-effects model represent the final analysis of the meta-analysis (yellow point), and the horizontal bar represents the 95%CI (Average). The numbers on the vertical axis represent the selected studies coded according to Table 5.

Another factor to consider is the statistical analysis that is used to demonstrate the possible association of the infection with the development of the disease since in most of the studies a logistic regression analysis was carried out; however, the use of a more specific methodology such as that shown by Mendonça *et al.* (2013) could show consistent data in this type of research.

Other essential factors such as the stimulation of cytokine production during parasitic infection should be considered as it is known that helminths can produce different products that can stimulate the production of immunomodulatory cytokines such as IL-10 (Maizels, 2020; Abdoli *et al.*, 2022). Proteomics and genomics studies have shown that *T. canis* can produce an onchocystatin protein (Soleyman *et al.*, 2020). This protein has been shown to induce IL-10 in other helminths and to be able to immunomodulator inflammatory responses and the production of transforming growth factor-â and parasite-specific IgG and IgG4 (Schönemeyer *et al.*, 2016).

Conclusions

- This study has shown a possible association between infection with *T. canis* and the development of asthma and the stimulation of IgE production. There are still gaps that need to be filled to understand better the relationship between this cosmopolitan infection and the development of one of the diseases with the most significant progress in the last three decades.
- Although the evidence is not entirely conclusive, the statistical analysis indicated a trend to consider *Toxocara* infection as a risk factor for the development of asthma. There are still several factors that in one way or another may be influencing these results, such as the lack of specific statistical analysis, and the lack of discrimination between atopic and non-atopic asthma.
- The association with specific IgE results supports previous findings in the literature, where helminth infections apparently stimulate the production of this type of antibody; however, more studies are need on SPT tests.

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