



Exposure to *Ascaris lumbricoides* infection and risk of childhood asthma in north of Iran

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Abstract

Background Asthma and *Ascaris lumbricoides* infection are common health issues affecting 250 and 700 million people worldwide, respectively. The relationship between ascariasis and asthma is a matter of substantial interest and research.

Methods We performed a case–control study to evaluate whether the exposure to *Ascaris* infection is associated with asthma in children. We also assessed potential risk factors for *Ascaris* infection and asthma in study area. We enrolled 145 asthmatic children and 115 healthy controls. The Global Initiative for Asthma guideline was used to evaluate asthma symptoms and severity in study participants. *Ascaris* infection was assessed by the presence of anti-*Ascaris* IgG ≥ 11 IU/mL measured by enzyme-linked immunosorbent assay.

Results We have found a significant relationship between exposure to *Ascaris* and asthma (odds ratio, 2.92; 95% CI 1.04–8.18; P value = 0.034), and this relationship remained significant after adjustment for covariates (adjusted OR, 3.36; 95% CI 1.04–13%; P value = 0.047). *Ascaris* infection was more frequent in children with mild sustainable asthma (13.2%; 15/113) than in children with moderate sustainable asthma (6.2%, 2/32), although there was a non-significant difference between these groups (OR, 2.3; 95% CI 0.5–10.1; P value = 0.35). Based on results of a multi-regression analysis, contact with soil (OR, 6.7; 95% CI 1.9–23.5), and drinking unsafe water (OR, 4.2; 95% CI 1.2–14.2) were significant risk factors for *Ascaris* infection in the study area.

Conclusion Results of this study suggest that *A. lumbricoides* infection might affect susceptibility to asthma in children. These results could be useful in prevention, early diagnosis and management of childhood asthma.

Keywords *Ascaris lumbricoides* · Relationship · Asthma · Children · Iran

Introduction

Asthma is one of the most prevalent non-communicable diseases worldwide, especially in lower income and less developed countries. Asthma is characterized by recurrent attacks of shortness of breath and wheezing, which vary in severity and frequency from person to person [1]. It is estimated that almost 250 million people around the world suffer from asthma [1]. According to the 2017 Global Burden of Disease Study, asthma was responsible for 495,100 deaths and approximately 23 million disability-adjusted life-years annually [2, 3]. While the causes of asthma are not completely understood, it is thought that a combination of genetic predisposition and environmental exposures is involved in the development of allergic disorders including asthma [4]. It has also been shown that some viral, bacterial, and parasitic organisms may be involved in the development and/or

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severity of asthma [5]. Among parasites, most investigations have focused on soil transmitted helminthes (STHs) including hookworms (*Ancylostoma* and *Necator*), whipworms (*Trichuris*), and roundworms (*Ascaris* and *Toxocara*) [6, 7].

Ascaris lumbricoides (Nematoda, Ascarididae) infects approximately 700 million people worldwide, with great disparity between regions and countries [8]. The incidence of *A. lumbricoides* infection is highest in Africa, Asia, the Caribbean region, and South America and lowest in Europe, North America, and Oceania [8]. In tropical and subtropical areas, children are often infected soon after birth, and poor sanitation, and crowded or high-density living conditions, as found in lower income, less developed regions, seem to be major risk factors of *A. lumbricoides* infection [8, 9]. Adult *A. lumbricoides* reside in the gut and eggs are passed in the host feces. These eggs embryonate in the environment and juvenile larvae develop in approximately 15 days; humans become infected when they ingest infective eggs. Following ingestion, eggs hatch in the small intestine and the juvenile penetrates the small intestinal mucosa and enters the circulatory system. Larvae that migrate to the lungs cause a transient inflammatory lung disease termed Loeffler's syndrome [10]. Several studies have reported that *A. lumbricoides* infection could be considered an environmental cause of allergic airway disease, an asthma phenotype, and inflammatory lung disease in developing countries [11–16]. It is hypothesized that *A. lumbricoides* modulates inflammatory responses (Th2-mediated allergic inflammation) and shared inflammatory responses that can result in asthma and other allergic disorders [17–19]. Other studies have suggested that accumulated levels of total and specific IgE induced by *A. lumbricoides* infection are linked to the development asthma [19, 20].

The previous observational studies have generally detected *A. lumbricoides* infection by microscopic examination of fecal samples. These methods have a high degree of specificity, but their sensitivity is low, especially in communities with low-level infections [18]. Serological methods to detect *A. lumbricoides*-specific antibodies, indicating active or prior infection, could be useful to better understand the association between *A. lumbricoides* and allergic disorders such as atopy and asthma [18]. It has been shown that anti-*Ascaris* IgE and IgG are useful markers for exposure to *A. lumbricoides* especially in areas of low prevalence [21, 22]. Several epidemiological investigations have explored the association between anti-*Ascaris* IgE and asthma symptoms, and most of these investigations demonstrated a significant positive association [13, 14, 23–25]; no studies have looked at an association between anti-*Ascaris* IgG and asthma. The goal of this study was to evaluate the association between *A. lumbricoides* infection and childhood asthma. We also assessed potential risk factors associated with *A.*

lumbricoides infection among children in the Mazandaran province of Northern Iran.

Materials and methods

Study design and population

This study included 145 asthmatic and 115 healthy children, 2–15 years, referred to the asthma and allergy clinic at Amirkola Hospital, the main pediatric hospital in the Mazandaran Province. Patients were physician-confirmed asthmatic children diagnosed according to the Global Initiative for Asthma (GINA) guidelines [26]. The following criteria were used to diagnose asthma: (1) repeated (three) episodes of wheezing, shortness of breath, coughing, and chest tightness, especially at night or in the early morning; (2) respiratory symptoms that improve spontaneously or after treatment; (3) the existence of triggers or aggravating factors such as exposure to allergens or irritants, physical exercise, weather changes, or emotional stress; and (4) a personal history of atopy (allergic rhinitis or eczema) and/or family history of atopy (asthma, allergic rhinitis, or eczema) in first-degree relatives. Controls were children from the same geographic region who attended the General Pediatric Outpatient clinic for routine health care and did not have physician-diagnosed asthma; controls had no personal or family history of atopy, had no gastrointestinal disorders, and had not been given any anti-parasitic drugs in the 6 months prior to the study. Children were excluded from the study if their parents or guardians did not have consent, if they had any other known medical condition, hepatosplenomegaly, generalized lymphadenopathy, or ocular symptoms. For all included children, the parents or legal guardians signed an informed consent and completed a standardized questionnaire that asked for data concerning socio-demographic characteristics (e.g., gender, age, and place of residence), risk factors for asthma, and history of exposure to *Ascaris* infection. All protocols for this study were approved by the Research Ethics Committee of the Babol University of Medical Science, Babol, Iran (no. IR.MUBABOL.HRI.REC.1396.207).

Sample collection and *Ascaris* serology

Sample collection was conducted between May and October 2018. A 3–5-mL sample of whole blood was drawn from each child. Blood samples were centrifuged at 1000g for 5 min, the serum collected and then transported on ice to the laboratory of Infectious Diseases and Tropical Medicine Research Center, where they were stored at – 20 °C until use.

Laboratory technicians performing ELISA were blind to the child's disease status. All sera were screened for anti-*A. lumbricoides* IgG antibodies using a commercial enzyme-linked immunosorbent assay (ELISA) kit (NovaTec Immunodiagnosics, Dietzenbach, Germany) following the manufacturer's instructions. The sensitivity and specificity for this kit have been reported to be > 95%. According to the manufacturer's recommendation, results were reported in International Units (IU). Sera with values of < 9.0, 9.0–11.0, and > 11.0 IU/mL were considered negative, suspect (gray zone), and positive, for antibodies to *A. lumbricoides*.

Statistical analysis

All analyses were done by SPSS Statistics software, version 21 (IBM, Armonk, NY, USA). The seroprevalences of *A. lumbricoides* infection in case and control groups were presented as relative percentages with binomial 95% confidence intervals (CI). To determine the association between exposure to *A. lumbricoides* infection and childhood asthma, Pearson's χ^2 and Fisher's exact tests (when expected frequencies were less than 5) were used for comparisons. Logistic regression with related odds ratios (ORs) and 95% CIs were used for multivariate analysis. In addition, the same methods were used to identify risk factors of asthma and for *A. lumbricoides* seropositivity. A *P* value < 0.05 was considered statistically significant.

Results

Table 1 shows the demographics of cases and controls and the prevalence of *A. lumbricoides* exposure each group and subgroup. One hundred and forty-five asthmatic children (80 boys and 65 girls) with a mean age of 6.88 ± 2.58 years were included the study. Ninety-nine (68%) of these children resided in an urban area. The majority of the children's parents (74%) had education levels of college or above). Family atopic history was identified in 60 (41.3%) of the children. Based on GINA guidelines, 113 (77.9%) children had mild persistent asthma, and 32 (22.1%) children had moderate persistent asthma. None of children had mild intermittent or severe persistent asthma. Controls included 115 healthy children (65 boys and 50 girls), with a mean age of 6.62 ± 3.63 . Cases and controls were comparable in terms of age and sex.

Overall, 22/260 children (8.4%; 95% CI 7.4–9.3%) tested positive for IgG antibodies to *A. lumbricoides*. Among these, 17 of the 145 asthmatic children (11.7%; 95% CI, 9.9–13.4%) and five of the 115 non-asthmatic children (4.3%; 95% CI 3.5–5%) were positive. In a Pearson's χ^2 test, *Ascaris* infection was significantly associated with asthma (OR, 2.92; 95% CI 1.04–8.18; *P* value = 0.034). In a multi-regression analysis and after adjustments for covariates, the

association was still significant (adjusted OR, 3.36; 95% CI 1.04–13%; *P* value = 0.047). *Ascaris* infection was more frequent in children with mild sustainable asthma (13.2%; 15/113) than in children with moderate sustainable asthma (6.2%, 2/32), although the difference was not significant (OR, 2.3; 95% CI 0.5–10.1; *P* value = 0.35). Mean total IgE was higher in *Ascaris*-infected children (234.06 ± 288.57) than in non-infected children (143.19 ± 218.05) in the case group. Analyses of other risk factors for asthma are presented in Table 2.

To better understand risk factors for exposure of children to *Ascaris* infection in the study area, we performed a statistical analysis considering different socio-demographic features. The results for univariate and multivariate regression analyses are presented in Table 3. Based on multi-regression analysis, contact with soil (OR, 6.7; 95% CI 1.9–23.5; *P* value < 0.001) and drinking unsafe water (OR, 4.2; 95% CI 1.2–14.2; *P* value = 0.015) was risk factors significantly associated with *Ascaris* infection.

Discussion

In this study, we assessed whether exposure to *A. lumbricoides* infection was associated with childhood asthma. Other studies have evaluated an association based on the presence of IgE antibodies specific to *A. lumbricoides*; to our knowledge, this is the first report of an association between anti-*Ascaris* IgG and increased morbidity due to asthma. Our results showed that *A. lumbricoides* infection could be a potential risk factor for the development of asthma in children. In agreement with our results, a previous meta-analysis reported that active *Ascaris* infection was a potential risk factor for asthma [6]. Other studies measuring the presence of *Ascaris*-specific IgE reported a significant association with bronchial hyper-responsiveness in Venezuela, wheezing in Ecuador and asthma in Colombia [27–29]. Similar to our study, Hagel et al. reported that bronchial hyper-reactivity in rural children was significantly associated with increased levels of anti-*Ascaris* IgE [27]. Moreover, a previous intervention study reported that deworming *Ascaris*-infected children improved clinical symptoms of asthma [30].

In the present study, we have found that the prevalence of IgG seropositivity to *A. lumbricoides* was higher in children with mild sustainable asthma than those with moderate sustainable asthma, although the difference was not significant. This may suggest that chronic exposures to ascariasis attenuate the severity of asthma. This result is in contrast with the previous studies on sensitization to *Ascaris* infection. Hunninghake et al. showed that sensitization to *Ascaris* was significantly related to increased severity of asthma among children in Costa Rica [25]. Similar results were reported by Buendía et al. where they reported that elevated levels of

Table 1 Demographic characteristics of children with asthma (cases) and healthy controls

Variable	Children with asthma (n = 145)		Children without asthma (n = 115)	
	Number (%)	Infected (%)	Number (%)	Infected (%)
Sex				
Male	80 (55.2)	12 (15)	65 (56.5)	3 (4.6)
Female	65 (44.8)	5 (7.6)	50 (43.5)	2 (4)
Age				
≤ 6	73 (50.3)	7 (9.5)	59 (51.3)	1 (1.69)
7–12	70 (48.3)	10 (14.2)	48 (41.7)	3 (6.25)
13–18	2 (1.4)	0 (0.0)	8 (7)	1 (12.5)
Residence				
Urban	99 (31.7)	7 (7.07)	60 (47.8)	2 (3.3)
Rural	46 (68.3)	10 (21.7)	55 (52.2)	3 (5.4)
Family income				
< 1500,000 T	87 (60)	12 (13.7)	83 (72.2)	4 (4.8)
≥ 1500,000 T	58 (40)	5 (8.6)	32 (27.8)	1 (3.1)
Contact with dogs				
Yes	8 (6.2)	1 (11.1)	14 (12.2)	0 (0.0)
No	137 (93.8)	16 (11.7)	101 (87.8)	5 (4.9)
Contact with cats				
Yes	2 (1.4)	0 (0.0)	3 (2.6)	0 (0.0)
No	143 (98.6)	17 (11.8)	112 (97.4)	5 (4.4)
Soil contact				
Yes	20 (13.8)	10 (50)	14 (12.2)	3 (21.4)
No	125 (86.2)	7 (5.6)	101 (87.8)	2 (1.9)
Eating unwashed vegetables				
Yes	11 (7.6)	4 (36.3)	6 (5.2)	1 (16.6)
No	134 (92.4)	13 (9.7)	109 (94.8)	4 (3.6)
Parents education				
Illiterate	2 (1.4)	1 (50)	2 (1.7)	0 (0.0)
Primary school	9 (6.2)	2 (22.2)	23 (20)	1 (4.3)
High school	69 (47.6)	9 (13.04)	68 (59.1)	2 (2.9)
College and above	65 (44.8)	5 (7.69)	22 (19.1)	2 (9.09)
Mother's occupation				
Housewife	119 (82.9)	16 (13.4)	107 (93)	4 (3.7)
Other	26 (17.1)	1 (3.84)	8 (7)	1 (12.5)
Father's occupation				
Government employment	143 (98.6)	17 (11.8)	105 (91.3)	5 (4.7)
Agricultural activities	2 (1.4)	0 (0.0)	10 (8.7)	0 (0.0)
Water source				
Treated	79 (54.5)	5 (6.3)	103 (89.6)	3 (2.9)
Untreated	66 (45.5)	12 (18.1)	12 (10.4)	2 (1.6)
Parents smoking				
Yes	29 (20)	4 (13.7)	38 (33)	0 (0.0)
No	116 (80)	13 (11.2)	77 (67)	5 (6.4)

anti-*Ascaris* IgE were positively related to clinical indicators of asthma severity [14].

The pathogenic mechanisms associated with *A. lumbricoides* infection and the development of allergic disorders including asthma are not well defined, and require further

investigation. *Ascaris* infection could have both immunostimulatory and immunosuppressive effects on the Th2 response, which is a critical mechanism involved in allergic disorders [31]. These stimulant or suppressive effects depend on many variables including host genetic background and the

Table 2 Univariate and multivariate analyses of asthma risk factors among case patients and controls

Variable	Children with asthma (n = 145) Number (%)	Children without asthma (n = 115) Number (%)	Univariate analyses ORs (95% CIs)	Multivariate analyses ORs (95% CIs)
Sex				
Male	80 (55.2)	65 (56.5)	1	1
Female	65 (44.8)	50 (43.5)	1.06 (0.65–1.73)	1.07 (0.61–1.88)
Age				
≤ 6	73 (50.3)	59 (51.3)	1	1
7–12	70 (48.3)	48 (41.7)	1.18 (0.71–1.95)	1.08 (0.62–1.91)
13–18	2 (1.4)	8 (7)	0.20 (0.04–0.99) ^a	0.16 (0.02–0.78) ^a
Residence				
Urban	99 (31.7)	60 (47.8)	1	1
Rural	46 (68.3)	55 (52.2)	0.51 (0.31–0.84) ^a	0.66 (0.36–1.2)
Family income				
≥ 1500,000 T	58 (40)	32 (27.8)	1	1
< 1500,000 T	87 (60)	83 (72.2)	0.58 (0.34–0.98) ^a	0.90 (0.48–1.71)
Contact with dogs				
No	137 (93.8)	101 (87.8)	1	1
Yes	8 (6.2)	14 (12.2)	0.42 (0.17–1.04)	0.48 (0.16–1.39)
Contact with cats				
No	143 (98.6)	112 (97.4)	1	1
Yes	2 (1.4)	3 (2.6)	0.52 (0.09–3.18)	1.76 (0.17–16.5)
Soil contact				
No	125 (86.2)	101 (87.8)	1	1
Yes	20 (13.8)	14 (12.2)	1.15 (0.55–2.40)	1.02 (0.38–2.7)
Parents education				
College and above	65 (44.8)	22 (19.1)	1	1
High school	69 (47.6)	68 (59.1)	0.34 (0.04–2.55)	0.48 (0.24–0.93)
Primary school	9 (6.2)	23 (20)	0.34 (0.19–0.62)	0.22 (0.8–0.59)
Illiterate	2 (1.4)	2 (1.7)	0.34 (0.19–0.62)	0.31 (0.03–2.98)
Mother's occupation				
Other	26 (17.1)	8 (7)	1	1
Housewife	119 (82.9)	107 (93)	0.34 (0.15–0.78)	0.70 (0.42–1.12)
Father's occupation				
Government employment	143 (98.6)	105 (91.3)	1	1
Agricultural activities	2 (1.4)	10 (8.7)	0.15 (0.03–0.68)	0.26 (0.04–1.11)
Parents smoking				
No	116 (80)	77 (67)	1	1
Yes	29 (20)	38 (33)	0.51 (0.29–0.89)	0.56 (0.3–1.04)
<i>Ascaris lumbricoides</i> infection				
No	128 (88.3)	110 (95.7)	1	1
Yes	17 (11.7)	5 (4.3)	2.92 (1.04–8.18) ^a	3.36 (1.04–13) ^a

^aStatistically significant

intensity of infection. It has been shown that low-level exposure to *Ascaris* larvae increase IgE production, eosinophilia, and other Th2 inflammatory cytokines [29]. In addition, direct exposure to *Ascaris* antigens can induce IgE-mediated reactions in the lung, leading to asthma-like symptoms [32]. In a recent study, Weatherhead et al. concluded that *Ascaris* infection in humans can lead to a persistent allergic airway

disease that resembles human asthma. In their study, it was shown that *Ascaris* larval migration resulted to significant airway hyper-responsiveness, type-2 inflammatory infiltration, and early airway remodeling which resembles an extreme form of allergic airway disease [11]. They reported that *Ascaris*-infected mice had more robust type-2 cytokine responses (IL4, IL5, and IL13) in both the bronchoalveolar

Table 3 Univariate and multivariate analyses of risk factors associated with *Ascaris lumbricoides* infection among children in northern Iran

Variable	All children (<i>n</i> = 260)		Univariate OR (95% CI)	Multivariate OR (95% CI)
	<i>N</i>	Infected (%)		
Sex				
Male	145	15 (10.3)	1	1
Female	115	7 (6)	0.56 (0.22–1.43)	0.54 (0.17–1.67)
Age				
≤ 6	132	8 (6)	1	1
7–12	118	13 (11)	1.92 (0.77–4.80)	2.09 (0.68–6.38)
13–18	10	1 (10)	1.72 (0.19–15.33)	1.86 (0.12–30.08)
Residence				
Urban	159	9 (5.6)	1	1
Rural	101	13 (12.8)	2.46 (1.01–5.99) ^a	1.81 (0.59–5.53)
Family income				
< 1500,000 T	170	16 (9.4)	1.45 (0.55–3.86)	0.95 (0.26–3.45)
≥ 1500,000 T	90	6 (6.6)	1	1
Soil contact				
Yes	34	13 (38.2)	14.93 (5.71–39.01) ^a	14.04 (4.62–42.67) ^a
No	126	9 (7.1)	1	1
Eating unwashed vegetables				
Yes	17	5 (29.4)	3.85 (1.14–13.02)*	2.23 (0.44–11.16)
No	243	17 (6.9)	1	1
Parents education				
Illiterate	4	1 (25)	3.80 (0.35–41.63)	20.66 (1.30–329.43)
Primary school	32	3 (9.3)	1.18 (0.29–4.88)	0.69 (0.11–4.22)
High school	137	11 (8)	0.10 (0.37–2.68)	1.37 (0.36–5.22)
College and above	87	7 (8)	1	1
Water source				
Treated	182	8 (4.3)	1	1
Untreated	78	14 (17.9)	4.76 (1.91–11.87)*	3.80 (1.29–11.17) ^a

^aStatistically significant

lavage fluid and lung tissue in comparison with un-infected mice. Moreover, increased levels of IL-17, a Th17 cytokine that is related to the severity of allergic airway disease, was observed in *Ascaris*-infected mice [11]. Results from other animal studies further support the effects of *A. lumbricoides* infection on host lung [33–35]. Likewise, experimental studies have indicated that some antigenic components of *A. suum* have modulating effects on the immune response of the host, mediated through an IL-10-dependent mechanisms [36]. This study showed that the co-immunization of mice with ovalbumin and *A. suum* antigenic components led to a delayed type hypersensitivity (DTH) to ovalbumin and suppression of immune responses to ovalbumin including the production of specific antibodies such as IgE and anaphylactic IgG1 [37–42]. An active component of the high molecular weight fraction of *A. suum* body fluid, a 200-kDa protein called PAS-1, appeared to be responsible for these effects [43]. It also appeared that elevated production of IL-10 had a key role in the suppressive effects of PAS-1 on Th2 responses and may downregulate the antigen-presenting

ability of dendritic cells [44, 45]. PAS-1 downregulates Th2 responses associated with the development of asthma in mouse models of *A. suum*-induced and ovalbumin-induced asthma [44, 46].

In the past decades, there has been a significant downward trend in the incidence of STHs in Iran, mainly due to improvement of sanitary conditions. Despite this, STHs are still prevalent, especially in the northern parts of Iran, where climatic conditions are suitable, the rural population is large, and agriculture and animal husbandry activities are common [47]. In this study, we assessed risk factors associated with *Ascaris* seropositivity among children in North of Iran. In a multivariate analysis, we have found that contact with soil and drinking unfiltered water were potential risk factors; furthermore, in a univariate analysis, eating unwashed vegetables and residing in a rural area were additional risk factors for *Ascaris* seropositivity. The northern part of Iran is an endemic area for many intestinal parasites, although in recent years and following sustainable improvement in public health systems, there

has been a significant decreasing trend in the prevalence of intestinal parasites in this area [48–51]. Nevertheless, we found that 8.4% of children in this study were exposed to *Ascaris* infection. The previous studies in this area showed a moderate level of contamination of vegetables with *A. lumbricoides* ova [52, 53]. In addition, a higher rate of intestinal parasite infection in rural communities in this area has reported [54–56]. This latter observation could be explained by more contact with soil by children in rural areas, by the availability of unsafe drinking water and other sources of infection. In agreement with this statement, several studies have reported the roles of soil and unsafe drinking water in the transmission of intestinal parasites including *A. lumbricoides* [57–59].

Our study has several limitations. We were unable to gather stool samples from children; therefore, it could not be determined whether seropositive children had past or active *Ascaris* infection. In addition, we were unable to perform *A. lumbricoides* IgE sensitization studies or to determine total IgE. In conclusion, despite the aforementioned limitations, the results of this study demonstrate that *A. lumbricoides* infection might affect the development of asthma in children. Due to the low sample size in this study and also the low number of children with *Ascaris* infection (17 and 5, among cases and controls, respectively), our results should be interpreted with caution. However, the results suggest a need for additional investigations with larger sample sizes and further analyses (i.e., stool examination, IgE sensitization) to further elucidate this relationship. In addition, based on our report of risk factors for ascariasis among children in North of Iran, we suggest improved health education and preventive measures to avoid exposure to *A. lumbricoides* infection in children.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants parents included in the study.

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