

Wheezing, Allergy, and Parasite Infection in Children in Urban and Rural Ethiopia

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Epidemiological studies in developing countries suggest that intestinal parasite infection may reduce the risk of asthma. Because this evidence is all derived from adults and older children, we have investigated the relation between parasite infection, wheezing, and allergen skin sensitization in nested case-control studies drawn from a survey of 7,155 children aged 1 to 4 years living in urban and rural areas of Jimma, Ethiopia. Infection with parasites was common, predominantly with *Trichuris* (54%), *Ascaris* (38%), and hookworm (10%). Wheezing in the past year was significantly more prevalent in urban (4.4%) than rural children (2.0%), and was less prevalent in those infected with *Ascaris* (age, sex, and urban/rural adjusted odds ratio, 0.5; 95% confidence interval, 0.3 to 0.9), particularly in relation to high-intensity infection. Similar, although nonsignificant, associations were found for hookworm (adjusted odds ratio, 0.6; 95% confidence interval, 0.2 to 1.8), but there was no suggestion of any relation to *Trichuris* infection. *Dermatophagoides pteronyssinus* and cockroach (*Blattella germanica*) skin sensitization was more prevalent in rural than urban children, and was unrelated to wheeze. We conclude that *Ascaris* and possibly hookworm infection protects against wheeze in young Ethiopian children, and that this effect is not mediated by inhibition of allergen sensitization.

Keywords: atopy; parasites; wheeze

There is now increasing interest in the hypothesis that the low prevalence of asthma and other allergic disorders observed in tropical rural subsistence societies may be attributable, at least in part, to a protective effect of intestinal parasite infection (1–4). This hypothesis was first proposed in the 1970s, when several studies commented on the apparent inverse relation between parasite infection and various markers of allergy or allergic disease in tropical developing countries (5–12), but subsequent evidence was less supportive and in 1985 an authoritative review concluded that the data “neither refute nor support the theory that parasite infection protects against asthma” (13). However three more recent studies have again demonstrated a clear inverse relation between intestinal parasite infection and markers of atopy or allergic disease in tropical, economically developing societies (14–16), and our own work in Ethiopia has in particular suggested that part of the explanation for earlier inconsistencies in the evidence (13) may be that protection against allergy arises primarily from parasites with a systemic phase in their life cycle (16).

To date, however, all of the available evidence is derived from studies of adults or school-age children, and there are no published data from younger children. Because the early years of life are an especially important period in the development of allergic disease (17, 18), and are the years in which many children are first exposed to parasite infections, it is important to explore the relation between allergic disease and parasite infections in this period of life. We have therefore investigated the relation between wheezing illness, allergen skin sensitization, and intestinal parasite infection in children aged 1 to 4 years in urban and rural areas of Jimma, in southwest Ethiopia.

METHODS

In late 2000/early 2001 we surveyed all children aged 1 to 4 years living in Jimma Town and three rural communities (Shebe, Agaro, and Asendabo), obtaining respiratory symptoms and lifestyle data from parents, usually the mother, by a field worker-led Amharic questionnaire derived from the International Study of Asthma and Allergies in Childhood (ISAAC) Study (19) and our previous survey in Jimma (20). Allergen skin tests for *Dermatophagoides pteronyssinus* and *Blattella germanica* (cockroach), with saline and histamine controls (Biodiagnostics, Upton-upon-Severn, UK), were performed on all consenting children and positive tests were defined as a mean wheal diameter of 2 mm or more. Because precise dates of birth were rarely known, age was estimated from the reported year of birth.

We defined three separate case groups, respectively comprising all children with (1) wheeze in the last year, (2) positive skin tests to *D. pteronyssinus*, and (3) positive skin tests to cockroach. We requested fecal samples for parasite estimation in a 10% systematic sample of all children, and from all cases. Because of a protocol misunderstanding, field workers also obtained fecal samples from all children with positive histamine skin tests, without recording whether they were part of the systematic sample. To correct for this we took a post-hoc random subsample of histamine-positive individuals to obtain a final cross-sectional subsample of individuals with parasite data that was representative of the total survey population in terms of all skin test responses, and wheeze. We used this representative subsample to describe the pattern of parasitic infection and define tertiles of infection intensity in the general population, and as the source of three control groups comprising those (1) without wheeze, (2) skin test negative to *D. pteronyssinus*, and (3) skin test negative to cockroach, for comparison with the respective case groups defined above in case-control analyses (Figure 1). Fecal parasites were analyzed by formalin–ether sedimentation (21) and infection was categorized qualitatively according to the presence or absence of eggs in the fecal sample, and quantitatively by tertiles of eggs per gram.

The relation between parasite infection and wheeze or allergen skin sensitization was analyzed by logistic regression, adjusting for age, sex, and rural or urban residence. Potential confounding by parental educational status (the higher of the mother and father), parental occupation, parental smoking, sibship size, and housing style, and interactions with site of residence, were also explored. When we planned the study we did not know precisely how many children lived in the study areas or how many would qualify for the three case groups, but from local anecdotal estimates and previous data in older children (20) we expected to recruit about 500 cases of wheeze and 500 skin tests positive to each allergen, which with control groups of 1,000 would provide 90% power to detect a trend in risk through increasing tertiles of parasite load with an odds ratio of 0.5 for the highest compared with

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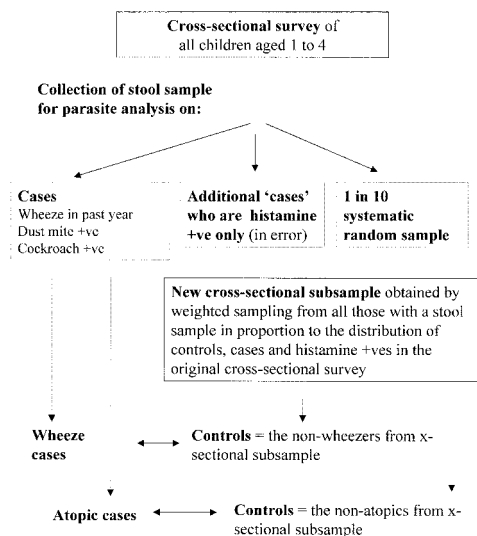


Figure 1. Sampling methodology and the identification of cases and controls.

the lowest. In the event, the wheeze case-control sample obtained in the study (617 individuals) actually provided 80 and 90% power to detect an odds ratio for presence of parasite infection of 0.5 and 0.4, respectively.

RESULTS

A total of 7,155 children, 60% from the urban area and 51% female, were identified and participated in the survey. Because there are no reliable census data on the number of children living in Jimma District the precise response rate is not known, but anecdotally there were few refusals. There was a relatively low proportion of children reported to be aged 1 year, and a high proportion of children reported to be aged 4 years (Table 1). Wheeze in the past year was reported in 246 (3.4%) children, increased slightly with age (Table 2), was slightly more common in boys than girls (odds ratio [OR], 1.2; 95% confidence interval [95% CI], 1.0 to 1.6), and was significantly more common in the urban than rural area (OR, 2.2; 95% CI, 1.6 to 3.0). Skin sensitization to *D. pteronyssinus* was present in 273 (3.8%) children, was less clearly related to age (Table 2), was unrelated to sex, and was substantially less common in the urban area (OR, 0.1; 95% CI, 0.1 to 0.2). Skin sensitization to cockroach was present in 420 (5.9%) children, and was also much less common in the urban area (OR, 0.4; 95% CI, 0.3 to 0.4). There was no significant association between wheeze and sensitization to either allergen.

Approximately 44% of children identified as cases and/or in the systematic sample provided a fecal sample for parasite estimation, with more provided from the urban area and from older children. Fecal parasite data were available in a cross-sectional subsample of 563 children, which included 18 wheeze cases, 20 *D. pteronyssinus* cases, and 32 cockroach atopic cases (Table 1). Sixty-nine percent of children had at least one parasite, and 33 and 6% had more than one and more than two parasites, respectively. The most common parasite infection was *Trichuris trichiura*, which was present in 54% of the cross-sectional sample, followed by *Ascaris lumbricoides* (38%), and hookworm (*Necator americanus*) in 10%. *Schistosoma*, *Enterobius*, and *Hymenolepis* were rare, occurring in 1.6, 0.5, and 4.4%, respectively, and have not been analyzed further. The prevalence of infection with parasites was similar in boys and girls (all $p > 0.4$) and increased with age in both rural and urban areas (Table 2). *Trichuris* was

more prevalent in urban children, *Ascaris* and hookworm were more common in rural children, and hookworm was particularly rare in the urban area. The intensity of infection ranged from 1 to 14,290 (median, 75.5) eggs/g for *Trichuris*, from 2 to 31,378 (median, 167) eggs/g for *Ascaris*, and from 3 to 895 (median, 30) eggs/g for hookworm. Individuals with a high intensity of infection with any one parasite tended to be infected with multiple parasites.

Fecal parasite data were available from 72 wheezing cases, respectively, 130 and 215 cases sensitized to *D. pteronyssinus* and cockroach. In the wheeze case-control group, the presence of *Ascaris* was associated with a significantly reduced risk of wheeze (age, sex, and urban or rural site adjusted OR, 0.5 [95% CI, 0.3 to 0.9], which was intensity related) ($p = 0.01$, Table 3). The magnitude of these effects was unchanged after controlling for other potential confounding factors, and although markedly stronger in the urban area (OR, 0.3; 95% CI, 0.1 to 0.7) than in the rural area (OR, 1.0; 95% CI, 0.4 to 2.4), the interaction was not significant ($p = 0.1$). The presence of hookworm was also associated with reduced risk of wheeze (OR, 0.6; 95% CI, 0.2 to 1.8), the reduction being greatest in the highest tertile of infection intensity (OR, 0.4; 95% CI, 0.00 to 3.0), but these effects were not statistically significant. *Trichuris* infection was unrelated to wheeze (OR, 1.1; 95% CI, 0.6 to 1.8) and there was no indication of any relation with infection intensity. The number of different parasites present in an individual was weakly and negatively associated with the risk of wheeze ($p = 0.09$), but this effect disappeared after allowing for the intensity of *Ascaris* infection.

There was no relation between any parasite infection and sensitization to *D. pteronyssinus* (OR for infection with *Ascaris*, 1.1 [95% CI, 0.7 to 1.7]; OR for infection with hookworm, 1.2 [95% CI, 0.7 to 2.0]; OR for infection with *Trichuris*, 1.4 [95% CI, 0.9 to 2.2]). Sensitization to cockroach was increased in those with *Trichuris* infection (OR, 1.7; 95% CI, 1.1 to 2.4), but was not dose related and was significant only in the rural population (interaction p value = 0.009). There was no relation between cockroach sensitization and infection with either *Ascaris* (OR, 1.0; 95% CI, 0.7 to 1.4) or hookworm (OR, 1.3; 95% CI, 0.8 to 2.2).

DISCUSSION

This study is to our knowledge the first to explore the relation between parasite infection and wheeze and allergy in very young children in a developing country. The populations we studied came from urban and rural areas of southwest Ethiopia at a relatively early stage of economic development. The urban area of Jimma Town has a population of about 80,000, no major industry, little motorized transport, a diet based on locally produced crops and animals, and housing of traditional or low-cost materials. The rural areas around Jimma are populated by subsistence farming communities living a traditional Ethiopian lifestyle with virtually no economic development. Our study shows that although rare by comparison with developed countries (22, 23), wheezing is present in young children in this developing country environment, and is much more common in urban than rural areas. Our skin test data show that *Dermatophagoides pteronyssinus* and cockroach sensitization is also present in young children in Jimma but is not significantly related to wheeze, and in contrast with wheeze is much less common in the urban area. These findings are entirely consistent with our previous data on the prevalence of asthma and atopy in older children and adults in Jimma (20).

Parasite infections are common in adults and older children in the Jimma communities (16) and because access to medical services is extremely limited, few people are treated for parasitosis and those that are treated will become infected again relatively quickly. Our parasite data show that infection is also common in children under 5 years of age, although in relation to adults in

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE SURVEY PARTICIPANTS AND THE CROSS-SECTIONAL SUBSAMPLE WITH PARASITE MEASUREMENT

	All Survey Participants			Cross-sectional Subsample*		
	Urban n (%)	Rural n (%)	All n (%)	Urban n (%)	Rural n (%)	All n (%)
Total	4,285	2,870	7,155	390	173	563
Age, yr						
1	366 (8.5)	461 (16.1)	827 (11.6)	34 (8.7)	26 (15.0)	60 (10.7)
2	1,122 (26.2)	660 (23.0)	1,782 (24.9)	78 (20.0)	30 (17.3)	108 (19.2)
3	1,100 (25.7)	541 (18.9)	1,641 (22.9)	86 (22.1)	38 (22.0)	124 (22.0)
4	1,388 (32.4)	661 (23.0)	2,049 (28.6)	159 (40.8)	55 (31.8)	214 (38.0)
Missing	309 (7.2)	547 (19.1)	856 (12.0)	33 (8.5)	24 (13.9)	57 (10.1)
Male	2,113 (49.3)	1,419 (49.4)	3532 (49.4)	187 (47.9)	88 (50.9)	275 (48.8)
Female	2,172 (50.7)	1,451 (50.6)	3623 (50.6)	203 (52.1)	85 (49.1)	288 (51.2)
Parental education						
Higher	825 (19.3)	17 (0.6)	842 (11.8)	15 (3.8)	98 (56.6)	113 (20.1)
Grades 7–12	2,315 (54.0)	274 (9.5)	2,589 (36.2)	92 (23.6)	59 (34.1)	151 (26.8)
Grades 1–6	985 (23.0)	1,022 (35.6)	2,007 (28.1)	217 (55.6)	14 (8.1)	231 (41.0)
No education	157 (3.7)	1,557 (54.3)	1,714 (24.0)	66 (16.9)	2 (1.2)	68 (12.1)
Missing	3 (0.1)	0	3 (0.0)	0	0	0
Sibship size						
0	1,250 (29.2)	362 (12.6)	1,612 (22.5)	100 (25.6)	23 (13.3)	123 (21.8)
1 or 2	1,865 (43.5)	1,159 (40.4)	3,024 (42.3)	176 (45.1)	68 (39.3)	244 (43.3)
3 or more	1,170 (27.3)	1,349 (47.0)	2,519 (35.2)	114 (29.2)	82 (47.4)	196 (34.8)
Housing						
Type of roof						
Corrugated iron	4,147 (96.8)	878 (30.6)	5,025 (70.2)	378 (96.9)	51 (29.5)	429 (76.2)
Thatched	123 (2.9)	1,970 (68.6)	2,093 (29.3)	11 (2.8)	120 (69.4)	131 (23.3)
Brick	15 (0.4)	22 (0.8)	37 (0.5)	1 (0.3)	2 (1.2)	3 (0.5)
Type of wall						
Mud	3,827 (89.3)	2,462 (85.8)	6,289 (87.9)	358 (91.8)	140 (80.9)	498 (88.5)
Wood/cement	458 (10.7)	408 (14.2)	866 (12.1)	32 (8.2)	33 (19.1)	65 (11.5)
Type of floor						
Mud	2,751 (64.2)	2,842 (99.0)	5,593 (78.2)	257 (65.9)	171 (98.8)	428 (76.0)
Covered/built	1,534 (35.8)	28 (1.0)	1,562 (21.8)	133 (34.1)	2 (1.2)	135 (24.0)
Wheeze in the past year	188 (4.4)	58 (2.0)	246 (3.4)	15 (3.8)	3 (1.7)	18 (3.2)
Skin test positive						
<i>Dermatophagoides</i>						
<i>pteronysinus</i>	51 (1.2)	222 (7.7)	273 (3.8)	4 (1.0)	16 (9.2)	20 (3.6)
Cockroach	154 (3.6)	266 (9.3)	420 (5.9)	10 (2.6)	22 (12.7)	32 (5.7)

* Cross-sectional subsample with parasite data.

Jimma (16) infection with hookworm is relatively rare in these young children, particularly in the urban area. We have shown that infection with *Ascaris* in young children is associated with a significantly reduced risk of wheeze, and although not significant in the present study, similar findings pertain to infection with hookworm. There was no evidence of any reduction in risk of wheeze associated with infection with *Trichuris*. These findings are broadly consistent with our previous suggestion that

protection against allergic disease arises primarily from parasites with a systemic phase in their life cycle (16), but contrast with our previous finding in adults and older children that hookworm rather than *Ascaris* exhibited the stronger dose–response effect. Our findings are not consistent, however, with the study by Palmer and coworkers, who demonstrated a positive association between *Ascaris* and asthma among children from asthmatic families in China (24); the explanation for these findings is not clear.

TABLE 2. WHEEZE IN THE PAST YEAR, SKIN TEST SENSITIZATION, AND PARASITE INFECTION BY AGE

	Age				Total* n (%)
	1 yr n (%)	2 yr n (%)	3 yr n (%)	4 yr n (%)	
Wheeze	23 (2.8)	61 (3.4)	49 (3.0)	84 (4.1)	246 (3.4)
<i>Dermatophagoides</i>					
<i>pteronysinus</i> positive	30 (3.6)	52 (2.9)	72 (4.4)	78 (3.8)	273 (3.8)
Cockroach positive	37 (4.5)	87 (4.9)	108 (6.6)	121 (5.9)	420 (5.9)
Parasite infection in cross-sectional subsample†					
<i>Trichuris</i>	21 (35.0)	53 (49.1)	62 (50.0)	131 (61.2)	301 (53.5)
<i>Ascaris</i>	21 (35.0)	37 (34.3)	39 (31.5)	87 (40.7)	213 (37.8)
Hookworm	8 (13.3)	5 (4.6)	11 (8.9)	28 (13.1)	58 (10.3)

* n = 7,155.

† n = 563.

TABLE 3. RELATION BETWEEN PARASITE EGGS PER GRAM AND WHEEZING

Parasite	Range (eggs/g)	Cases		Controls		Adjusted Odds Ratio*	p Value†
		Urban n (%)	Rural n (%)	Urban n (%)	Rural n (%)		
<i>Ascaris</i>	No eggs	43 (84.3)	12 (57.1)	241 (64.3)	95 (55.9)	1	0.02
	Eggs detected	8 (15.7)	9 (42.9)	134 (35.7)	75 (44.1)	0.5 (0.3–0.9)	
Tertiles of eggs per gram	1–55	4 (7.8)	1 (4.8)	43 (11.5)	27 (15.9)	0.5 (0.2–1.2)	0.01
	56–413	3 (5.9)	7 (33.3)	34 (9.1)	35 (20.6)	0.8 (0.4–1.8)	
	> 413	1 (2.0)	1 (4.8)	57 (15.2)	13 (7.6)	0.2 (0.0–0.7)	
<i>Hookworm</i>	No eggs	51 (100)	16 (76.2)	364 (97.1)	123 (72.4)	1	0.4
	Eggs detected	0 (0)	5 (23.8)	11 (2.9)	47 (27.6)	0.6 (0.2–1.8)	
Tertiles of eggs per gram	1–17		2 (9.5)	3 (0.8)	17 (10.0)	1.3 (0.3–4.7)	0.2
	18–44		2 (9.5)	4 (1.1)	15 (8.8)	0.4 (0.0–2.9)	
	> 44		1 (4.8)	4 (1.1)	15 (8.8)	0.4 (0.0–3.0)	
<i>Trichuris</i>	No eggs	22 (43.1)	10 (47.6)	148 (39.5)	107 (62.9)	1	0.8
	Eggs detected	29 (56.9)	11 (52.4)	227 (60.5)	63 (37.1)	1.1 (0.6–1.8)	
Tertiles of eggs per gram	1–31	13 (25.5)	5 (23.8)	56 (14.9)	39 (22.9)	1.8 (1.0–3.2)	0.2
	32–180	9 (17.6)	5 (23.8)	81 (21.6)	18 (10.6)	0.9 (0.4–1.8)	
	> 180	7 (13.7)	1 (4.8)	90 (24.0)	6 (3.5)	0.5 (0.2–1.1)	

* Adjusted for age, sex, and urban or rural residence. Values in parentheses indicate 95% confidence interval.

† p Values for tertiles are given for the linear trend in risk across increasing tertiles.

In contrast to a previous study of *Schistosoma* infection (15), we found no statistically significant evidence that parasite infection reduced the risk of sensitization to *D. pteronyssinus* or cockroach; indeed, there was evidence of a higher risk of cockroach sensitization in those with *Trichuris* infection, although only in the rural community. In our previous study we reported evidence that parasite infection modified the effect of allergen sensitization on the risk of wheeze, apparently preventing the expression of wheeze in atopic individuals who were infected; we did not find evidence of this effect in these younger children.

This study was performed in an area where there is little information available on the local population structure, and the population is geographically diverse and isolated. We did not know the number of under-fives in the chosen study area and therefore do not have an accurate estimate of our participation rate, but because the number of participants was less than estimated at the outset our study had less power than we planned, and less than our previous studies in Jimma (16, 20). Because there are no reliable birth records for the majority of the target population we had to accept parental estimates of age (based on parent-reported year of birth and the calendar year of the survey) and this might account to some extent for the apparent respective under- and overrepresentation of children aged 1 and 4 years. The response rate for the provision of fecal samples for parasite estimation was relatively low but we are not aware of any systematic bias in relation to any of our exposures or outcomes. It is likely that, as in the developed world, a substantial proportion of the wheezing reported in these children was due to etiologies other than asthma, and this may explain to some degree the lack of association between wheeze and allergic sensitization, although our previous study suggested that parasite infection itself protected against the expression of wheeze in atopic individuals (16). There are few data available on the prevalence of skin sensitization in comparable age groups from developed countries, but the only study of which we are aware (from Estonia) reveals sensitization prevalences broadly similar to those in the present study (25).

Our study provides further evidence that systemic-phase parasites can protect against the manifestation of asthma, and demonstrates that this protection is afforded even in very young children. Although the mechanisms of this influence remain unknown, it

is likely that they involve either the enhanced production of antiinflammatory downregulatory molecules such as interleukin (IL)-10 and transforming growth factor- β (TGF- β) (4) and/or suppression of the proinflammatory interleukins IL-4 and IL-5 and eotaxin (26). Hookworm infections have also been shown to suppress host helper T cell type 2 (Th2) responses by secretion of a metalloproteinase that digests eotaxin (27), by induction of apoptosis in T lymphocytes (28), and by secretion of calreticulin, which inactivates C1q and subsequent inflammatory responses (29, 30), all of which have probably evolved to allow the parasite to survive the Th2-mediated host response to parasite infection but are also likely to inhibit the expression of allergic responses in infected individuals. Unfortunately, we were unable to make direct measures of cytokine or other markers of Th1/Th2 activity in the present study.

Whether exposure to parasites during the early stages of immune development sets the foundation for continued protection throughout life, or whether parasite protection can arise from infection at any age, is also not clear.

Our study also suggests that improved sanitation and consequent reductions in intestinal parasite infection may be one factor that has contributed to the rise in wheezing illness and other allergic disorders in developed and developing countries. Now that the protective effects of parasite infection have been demonstrated in several studies, it is perhaps now appropriate to try to establish whether this protection also applies if parasite infection is introduced after the early years of life, and whether (as first suggested nearly 30 years ago) this phenomenon can be applied to therapeutic benefit in asthma and other allergic diseases (31).

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