

Relationship between Different Species of Helminths and Atopy: A Study in a Population Living in Helminth-Endemic Area in Sulawesi, Indonesia

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Key Words

Skin prick test • Cockroach allergen • *Brugia malayi* • Lymphatic filariasis • Helminths, soil-transmitted

Abstract

Background: The association between allergen skin sensitization and helminth infection has been debated for years. Here, we sought to estimate the prevalence of atopic sensitization of residents living in area endemic for lymphatic filariasis and intestinal helminths and to investigate the association between these different species of helminths with allergen skin test reactivity to allergens. **Methods:** Five hundred and eighty-three individuals living in an area endemic for *Brugia malayi* and for intestinal helminths were skin prick tested using 3 allergens. Microfilariae were enumerated by filtration of 1 ml nocturnally collected blood, and 442 stool samples were examined for the presence of intestinal helminth eggs. **Results:** The prevalence of skin prick test positivity to any allergen was 23.5% (to cockroach 20.6%, to house dust mite 6.2% and to grass pollen 1.2%). Individuals with *B. malayi* infection had a significantly reduced risk for atopic reactivity to cockroach (adjusted odds ratio 0.56, 95% CI 0.35–0.88). In the same population, no association was found between the presence of intestinal helminths and any

skin test reactivity. **Conclusions:** In a general population, across all ages in a rural area of Indonesia, the prevalence of skin test reactivity to house dust mite is as low as in other non-affluent countries, and infection with *B. malayi* appears to reduce the risk of skin reactivity to cockroach. On the other hand, we found no association between infection with intestinal helminths and skin test reactivity to aeroallergens.

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Introduction

The prevalence of allergic diseases has increased not only in high income but also in low to middle income countries [1]. However, generally, the prevalence of allergic disorders is thought to be higher in urban than in rural settings, particularly in low to middle income countries [2]. A number of factors related to lifestyle and environmental exposure are thought to explain these observations. Among these, it has been proposed that increases in allergic disease may be related to the immunological effects of the decline in infectious diseases in high income countries and urban environments. In this regard, several associations between viral, bacterial and parasitic infections and allergies have been shown using

indirect measurements of infections. Antibodies to hepatitis A, to *Toxoplasma gondii* or *Helicobacter pylori* [3] as well as cellular responses to mycobacterial antigens [4] as markers of exposure to food-borne fecal or mycobacterial pathogens were shown to be inversely associated with prevalence of asthma or skin prick test (SPT) positivity. The only studies that have related the actual presence of infections to allergic disorders are those measuring viral or parasitic infections. Whereas respiratory viral infections have been shown to be associated with exacerbation of asthma [for review see, 5], parasitic helminth infections have often been shown to be negatively associated with allergic disorders [6–8]. However, the latter relationship is complex as a number of studies have indicated that helminth infections increase the risk of allergic sensitization, atopy and symptoms [9, 10]. It has been argued that the species of helminthes, load or chronicity of helminth infections may be important characteristics that determine whether allergic responses are suppressed or not [11, 12]. Helminth infections are of particular interest because they have strong immunoregulatory effects on their host [13] which lead to T-cell hyporesponsiveness and might thereby also affect responses to bystander allergens. Interestingly, the immune regulatory effects of helminth infections are often seen when infections are intense and chronic in nature [14].

Helminths are often treated as a homogenous group because they all induce a pronounced upregulation of Th2 responses, yet important interspecies differences exist. The degree of immunosuppression induced by different helminth species is likely to vary, because long-lived, tissue-dwelling parasites such as schistosomes or filarial worms are thought to induce stronger immunoregulatory responses than lumen-dwelling intestinal parasites [15].

The objectives of this study are to estimate the prevalence of atopic sensitization across all ages in residents of an area endemic for lymphatic filariasis and intestinal helminths (IHs) in Sulawesi, Indonesia, and to investigate the association between these different species of helminths and allergen skin test reactivity.

Materials and Methods

Study Population

This study is part of the screening survey prior to the start of an anti-filarial drug trial has been reported elsewhere [16] and was approved by the Commission of Medical Ethics, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia. The trial registration number is ISRTN 37962059.

Life-long residents of the Parigi-Moutong and Bonebolang districts in Sulawesi, Indonesia are the study population. These areas are endemic for anthropophilic *Brugia malayi* and for IHs [17]. The purpose of the study and the procedures involved were explained to all residents and only those granting informed consent were enrolled as study participants.

Parasitological Diagnostics

Blood collection to detect microfilariae (MF) took place between 20.00 and 23.00 h, in accordance with the periodicity of the MF in this area [17]. The MF prevalence rate was assessed by Nuclepore (Nuclepore Corporation, Pleasanton, Calif., USA) filtration of 1 ml venous blood.

Detection of filarial-specific IgG4 antibodies using BmR1 dipstick (Brugia Rapid™, kindly provided by Prof. Rahmah Noordin, Universiti Sains Malaysia) was performed on plasma samples as described previously [18].

Stool samples were collected and preserved in 10% formaldehyde. In the laboratory at Jakarta direct examination of stools was performed to detect eggs of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm eggs.

Skin Prick Testing

Skin test reactivity for aeroallergens was performed with extracts of *Blattella germanica*, *Dermatophagoides pteronyssinus*, and *Dactylis glomerata* grass pollen (kindly provided by HAL Allergy Group, Leiden, The Netherlands). Histamine chloride (10 mg/ml) was used as the positive control and allergen diluent as negative control (kindly provided by HAL Allergy Group). SPT was done on the volar side of the lower arm, using disposable individual lancets (HAL Allergy Group), positioned at a 90° angle to allow each drop to penetrate only 0.1–0.2 mm into the skin. The longest diameter (D1) and the diameter perpendicular to it (D2) of the wheal were measured after 15 min. A SPT was considered positive when $D1+D2/2 \geq 3$ mm. The same investigator performed all the SPTs.

Statistical Analysis

Statistical analysis was performed in SPSS for Windows version 16. Comparison of proportions was performed using the χ^2 test. Differences between variables for 2 groups were assessed by Mann-Whitney U test. Logistic regression was used to analyze the association between the presence of parasite and skin test reactivity. Relative risks obtained by logistic regression are expressed in odds ratio (OR) and 95% confidence intervals (95% CI) are given. An OR of <1 indicates that the studied variable is negatively associated with the outcome, whereas an OR of >1 represents a positive association. Bonferroni correction is indicated for multiple testing.

Results

Study Subjects

SPT was performed in 583 subjects of whom 574 were examined for clinical and parasitological signs of filariasis. Stool samples were collected from 442 subjects of whom 441 were examined for the presence of IH eggs.

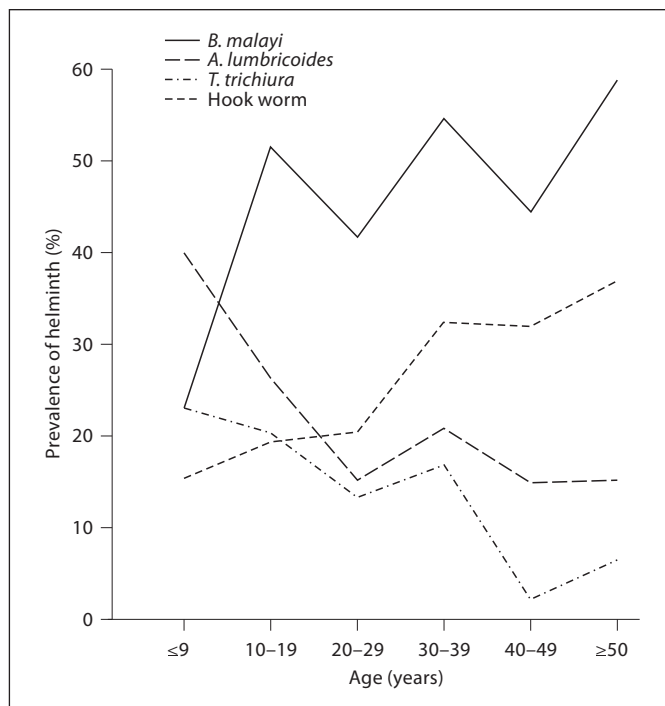


Fig. 1. Prevalence of *A. lumbricoides*, *T. Trichiura*, hookworm and *B. malayi* in different age groups.

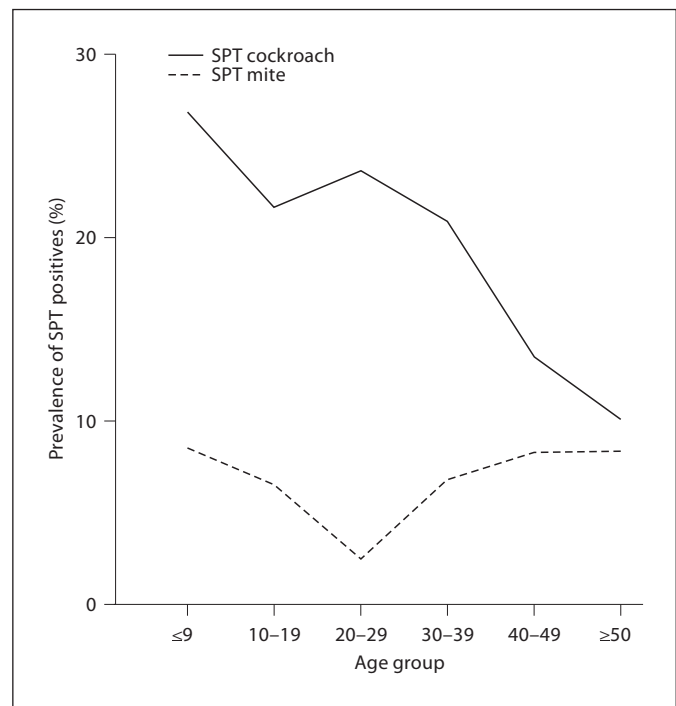


Fig. 2. Prevalence of SPT positive to mite and cockroach in different age groups.

Table 1. Prevalence of microfilaremia and clinical disease

Group	Number of subject (males/females)	Median age (range)	GM Mf/ml (range)	BR positivity/ number tested
AMF	292 (110/182)	23 (2–74)	–	109/224 (48.7%)
MF	260 (135/125)	26 (3–76)	231 (1–5,761)	126/135 (93.3%)
Lymph+MF	5 (1/4)	36 (12–70)	185 (1–1,684)	1/1 (100%)
Lymph+AMF	17 (5/12)	40 (15–64)	–	4/10 (40%)
Total	574 (251/323)	23 (2–90)	171 (1–5,761)	240/370 (64.9%)

AMF = Amicrofilareemics; MF = microfilareemics; Lymph = lymphoedema; GM = geometric mean; BR = Brugia Rapid test.

Prevalence of Microfilaremia and Clinical Signs

The number of microfilaremic individuals increased with increasing age (χ^2 test, $p = 0.001$; fig. 1). The proportion of microfilaremic patients was significantly higher in males (54.2%) compared to females (39.9%; χ^2 test, $p = 0.001$) as was the intensity of infection (geometric mean/ml 329 and 158 in males and females, respectively; $p = 0.004$). Clinical examination showed that 22 (3.8%) per-

sons (16 females and 6 males) had lymph edema of grades 1–3 (table 1). Five of them (1 male and 4 females) had MF in their night blood. The youngest individual with clinical disease was 12 years old and the oldest was 70 years old.

Brugia Rapid positive tests were found in 64.9% of the study population. The percentage of individuals with Brugia Rapid positivity was higher in males (71.5%) than in females (59.1%; χ^2 test, $p = 0.013$). The proportion of

Table 2. a Number and proportion of people by the presence of infection with *Ascaris lumbricoides*, hookworm, *Trichuris trichiura*, any intestinal helminth (IH), in people negative and positive skin prick test reactivity to cockroach, with OR for atopy, given helminth infection and 95% CI

Helminth infection		SPT- to cockroach		SPT+ to cockroach		Unadjusted OR (95% CI)	p value	Adjusted OR ¹ (95% CI)	p value
		n	%	n	%				
<i>A. lumbricoides</i>	No	283	78	60	74	1.27	0.36		
	Yes	78	22	21	26	(0.74–2.26)			
Hookworm	No	273	76	62	77	0.95	0.87		
	Yes	88	24	19	23	(0.54–1.68)			
<i>T. trichiura</i>	No	314	87	62	77	2.05	0.02	1.48 (0.79–2.76)	0.22
	Yes	47	13	19	23	(1.13–3.74)			
Any IH	No	208	58	41	51	1.35	0.23		
	Yes	153	42	40	49	(0.83–2.19)			
<i>B. malayi</i> MF ²	No	228	50	81	69	0.46	<0.001*	0.56 (0.35–0.88)	0.01*
	Yes	228	50	37	31	(0.30–0.70)			

* $p < 0.05$ after Bonferroni correction.

¹ Adjusted for district, age and sex.

² The presence of microfilariae (MF) was determined by filtration of night blood.

Brugia Rapid positivity in amicrofilaremic individuals either with or without clinical disease was 48.3%. Within microfilaremic individuals, Brugia Rapid positives were found in 93.4% of the samples (table 1).

Prevalence of Intestinal Helminth Infection

Of the 442 stool samples examined, the prevalence of *A. lumbricoides*, hookworm and *T. trichiura* was 22.4, 24.2 and 14.9%, respectively. The proportion of *A. lumbricoides* (χ^2 test, $p = 0.002$) and *T. trichiura* (χ^2 test, $p = 0.014$) positive individuals decreased with increasing age while the proportion of hookworm ($p = 0.015$) increased with increasing age (fig. 1). The percentage of hookworm (χ^2 test, $p = 0.03$) and *A. lumbricoides* (χ^2 test, $p = 0.06$) positive individuals was higher in males than in females. There were no differences in the prevalence of *T. trichiura* infection between females and males.

Skin Test Reactivity

Skin tests were performed for house dust mite, cockroach and grass pollen. The prevalence of skin reactivity to any allergen is 23.5% (137 of 583). Skin reactivity was predominantly found to cockroach (20.6%, 120 of 583) followed by mite allergen (6.2%, 36 of 583). Among 583 subjects, 3.8% (22 of 538) were positive for both cockroach and house dust mite. The prevalence of SPT positives for grass pollen was only 1.2% (7 out of 583).

The prevalence of skin test reactivity to cockroach tended to decrease with increasing age (fig. 2); however, this difference did not reach statistical significance.

Risk Factors for Skin Test Reactivity

A significant inverse association was observed between skin test reactivity to cockroach and *B. malayi* infection (OR 0.46, 95% CI 0.3–0.7, $p < 0.001$ or $p < 0.05$ after Bonferroni correction), and this association remained after controlling for confounding factors (OR 0.56, 95% CI 0.35–0.88, $p = 0.01$ or $p < 0.05$ after Bonferroni correction; table 2a). Furthermore, MF load in SPT-negative subjects (geometric mean MF/ml = 248) was significantly higher compared to SPT-positive subjects (median MF/ml = 146; $p < 0.001$).

A positive association was also found between skin test reactivity to cockroach and *T. trichiura* infection (OR 2.05, 95% CI 1.13–3.74, $p = 0.02$; table 2a); however, this association was no longer significant after controlling for potential confounders (OR 1.48 95% CI 0.79–2.76, $p = 0.22$). The skin reactivity to house dust mite was not associated with helminth infections (table 2b).

The prevalences of SPT positivity to cockroach in MF- and IH-, MF+ and IH-, MF- and IH+, and MF+ and IH+ subjects were 20.6, 10.6, 27.1 and 14.6%, respectively. These differences were statistical significant ($p < 0.05$).

Table 2. b Number and proportion of people by the presence of infection with *Ascaris lumbricoides*, hookworm, *Trichuris trichiura*, any intestinal helminth (IH), in people with negative and positive skin prick test reactivity to house dust mite (HDM), with OR for atopy, given helminth infection and 95% CI

Helminth infection		SPT– to HDM		SPT+ to HDM		Unadjusted OR (95% CI)	p value	Adjusted OR ¹ (95% CI)	p value
		n	%	n	%				
<i>A. lumbricoides</i>	No	328	78	15	71	1.41	0.49	2.30 (0.82–6.45)	0.11
	Yes	93	22	6	29	(0.53–3.73)			
Hookworm	No	320	76	15	71	1.25	0.66		
	Yes	101	24	6	29	(0.47–3.30)			
<i>T. trichiura</i>	No	361	86	15	71	2.37	0.09		
	Yes	60	14	6	29	(0.89–6.36)			
Any IH	No	239	57	10	48	1.43	0.43		
	Yes	182	43	11	52	(0.59–3.44)			
<i>B. malayi</i> MF ²	No	291	54	18	50	1.18	0.63		
	Yes	247	46	18	50	(0.60–2.31)			

¹ Adjusted for district, age and sex.

² The presence of microfilariae (MF) was determined by filtration of night blood.

Discussion

Based on the results of this study, we estimate that 23.5% of the population was atopic as determined by skin prick testing. Cockroach was the most common allergen causing sensitization followed by house dust mite. Sensitization to grass pollen was rare. Cockroach is recognized as one of the most important indoor allergen sources for the development of allergic diseases in inner cities in the USA [19]. In this study, and in accordance to a study in the USA [20], we found that skin reactivity to cockroach tended to decrease with increasing age.

The degree of sensitization to house dust mite was relatively low, at 6.2% for the whole population and 5.8% for the children aged 8–12 years. The low prevalence of skin reactivity to house dust mite in this study might be attributed to the fact that this study was conducted in a rural area of a non-affluent country [21]. The prevalence of SPT positivity is known to change with affluence, as well as in an urban to rural gradient, with the highest prevalence in urban rich followed by urban poor and lowest prevalence in rural populations [22]. The question remains whether *D. pteronyssinus* is the most appropriate source of allergen to detect mite allergy in this population. A study using different mite allergens in three cities of Mexico found that the frequency of skin reactivity to *Euroglyphus maynei* was higher in one city while skin reactivity to *D. pteronyssinus* and *D. farinae* was more fre-

quent in the two other cities [23]. The same applies to grass pollen, as the local grasses need to be identical with the source of allergen.

In this study we found that the prevalence of *Ascaris* and *Trichuris* was highest in the youngest age group (<10 years old) and decreased with increasing age. The age-related pattern of infection has been described for all major IHs in humans [24]. The age at which the maximum intensity of infection typically occurs is in 5- to 10-year-olds for *Ascaris* and *Trichuris* and in adults (>15 years) for hookworm [25]. The precise cause underlying this age-related profile is unknown but it is thought to involve age-related changes in exposure or susceptibility.

Epidemiological studies have found associations between allergen skin reactivity and IH infection. However, not all studies have shown an inverse association, some have provided evidence for positive associations while others showed no association [for review see, 26], between the presence of IHs and atopy. In this study, we found no association of skin test reactivity to cockroach and infection with 3 different IHs (*A. lumbricoides*, *T. trichiura* and hookworm). In the same population, however, we observed a strong negative association between infection with *B. malayi* and skin test reactivity to cockroach. Interestingly, we found that the prevalence of SPT positivity to cockroach was lowest in microfilaraemics with or without IH infections, indicating that filarial infection plays a major role in driving the negative association. An

inverse relationship between skin test reactivity to aeroallergens and infection with another filarial species, *Mansonella perstans*, has been reported in pregnant women in Uganda where the prevalence of infection was high at 21.3% [27]. However, a study in Gabonese children found no association of skin test reactivity and infection with filarial worms (*Loa loa* and *M. perstans*) but the prevalence of these infections was very low at 6% [28].

The finding in our study that the presence of filarial worms but not IHs was negatively associated with allergen skin test reactivity to cockroach may suggest that helminths that are confined to the intestinal lumen induce weaker immune regulatory effects compared to helminths that are systemic and reside in tissues. Adult *B. malayi* worms lodge in the lymphatic system, particularly lymphatic vessels and lymph nodes where they can live 4–6 years and produce millions of MF [29]. These worms have strong immunomodulatory activity, not only to specific antigens but also to unrelated antigens [30]. Within the microfilaraemics, MF count was higher in those negative for cockroach SPT, which might suggest that individuals with a heavier parasite burden have less atopy. We could not rule out the possibility that the intensity of IH infections plays a role as we only recorded the presence or absence of these infections. It has been suggested that the intensity of infection or heavy parasite burdens may induce downregulation of skin reactivity to allergens, whereas light infections might have the opposite effect [14].

Indeed, filarial and schistosome infections have been associated with upregulation of IL-10 production [31–33]. Anti-parasite IL-10 has been shown to be negatively associated with SPT responses [28]. Thus, it might be possible that a large amount of parasite-specific IL-10 leads to bystander suppression of the immune response to environmental allergens [33]. There may also be a direct effect of parasite products on mast cell degranulation, for

instance. A study has reported that mast cell degranulation is inhibited by the filarial parasite product, ES-62 [34].

The strength of this study is the relatively large population of all ages studied in areas where IHs and lymphatic filariasis are co-endemic, allowing us to explore the effects of 4 different species of helminths on skin reactivity to allergens. This study has several limitations and therefore the results should be interpreted with caution. Firstly, the study is cross-sectional in nature with no data on allergen exposure. Originally, the study was intended to look for the relationship between skin reactivity and filarial infection and therefore there is the possibility that we missed the potential relationships between skin reactivity and IHs. The presence of IHs was determined by a direct method which might not be sensitive enough to detect light infections.

In conclusion, this study shows that in a general population, across all ages in a rural area of Indonesia, the prevalence of skin test reactivity to house dust mite is low as reported for low-income countries and that infection with *B. malayi* appears to reduce the risk of skin reactivity to cockroach. On the other hand, we found no association between infection with IHs and skin test reactivity to aeroallergens.

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