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Original Article

Soil-transmitted helminth infection, intestinal permeability, and intestinal inflammation in preschool-age children

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Abstract

Background Soil-transmitted helminth (STH) infection is a major health problem in low-and middle-income countries (LMIC). The presence and activity of STH can cause changes in the intestinal mucosa, including cell damage that can affect intestinal permeability and stimulate immune responses such as inflammation.

Objective To assess the inflammatory and permeability status of the intestinal mucosa in various STH infections in preschool-age children residing in Nangapanda District, Ende Regency, East Nusa Tenggara.

Methods In this cross-sectional study, stool samples were obtained from children aged 12-59 months and examined for worm eggs using the Kato Katz method. Concentrations of biomarkers for intestinal permeability and inflammation were measured by enzyme-linked immunosorbent assay (ELISA). We measured fecal alpha-1-antitrypsin (AAT) as an intestinal permeability biomarker and fecal calprotectin (FC) as an intestinal inflammation biomarker and evaluated the association between these biomarkers with STH infection.

Results The prevalence of STH infection in 111 evaluated preschool-age children was 17.1%. Ascaris lumbricoides was the predominant species, followed by *Trichuris trichiura*. Most subjects (64.7%) had AAT levels >0.27 mg/g, while only 35.1% had FC >50 mg/kg. STH infection status was not significantly associated with AAT concentration status, even when analyzed by STH species. A significant association was found only between *T. trichiura* infection and FC concentration. In this study, which included infected and uninfected groups, children infected with *T. trichiura* had higher concentrations of FC than those uninfected.

Conclusion STH infection was not significantly correlated with fecal biomarkers except between *T. trichiura* infection status and increased gut inflammatory biomarker. The AAT levels were generally elevated in the evaluated preschool-aged population regardless of STH infection, indicating that other factors may have contributed to increased gut permeability. **[Paediatr Indones. 2025;65:232-8; DOI: https://doi.org/10.14238/pi65.3.2025.232-8**].

Keywords: *soil-transmitted helminth; preschool-aged children; intestinal permeability; mucosal inflammation*

Intestinal worm infections are common parasitic infections in humans, especially in developing countries with tropical and subtropical climates. The prevalence of soil-transmitted helminth (STH) infections in Indonesia ranges from 2.5% to 62%.[1] Children are one of the groups at high risk of STH infection. In 2022, the *World Health Organization* (WHO) reported that 23,700,681 preschool-aged and 46,868,763 school-aged children in Indonesia required preventive chemotherapy for STH infection.[2]

Ascaris lumbricoides infection is known to cause changes in the mucosal and muscular layers of the intestine, such as crypt hyperplasia and villous atrophy.[3] These changes will eventually impair the function of the intestine to absorb nutrients. Trichuris trichiura infection can also stimulate inflammatory responses in the intestinal mucosa, leading to increased epithelial permeability and susceptibility to invasion of other pathogens.[4,5] While STH infection has been shown to affect intestinal function through inflammation processes and changes in intestinal permeability, the impact of certain STH species on

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gut permeability and intestinal inflammation is still poorly understood.

Intestinal biopsy is considered the gold standard for detection of mucosal inflammation; it usually involves an endoscopic procedure that is known to cause discomfort to the patient. Therefore, biomarkers are more attractive proxies for inflammation to reduce invasive testing procedures.[6] One example of a biomarker that can be used to detect the presence of inflammation is fecal calprotectin (FC), a heterocomplex of two calcium and zinc-binding proteins, S100A8 and S100A9. These two proteins are expressed primarily in myeloid-derived cells such as granulocytes, monocytes, and early stages of macrophages. Therefore, the concentration of calprotectin in feces increases when inflammation occurs. Calprotectin is not damaged by proteolytic enzymes in the intestine and does not undergo reabsorption and metabolism, thereby ensuring its stability. Furthermore, calprotectin is well distributed in the feces.[7]

Alpha-1-antitrypsin (AAT) is a biomarker used to measure intestinal permeability. Most of these proteins are synthesized by hepatocytes and secreted into the bloodstream, then migrate to the lungs to protect the lining from neutrophil elastase.[8] The AAT can extravasate from the serum into the intestine when intestinal permeability increases. In the intestine, AAT is not reabsorbed and is metabolized to be excreted with feces. Therefore, it can be used as a biomarker for permeability of the intestinal mucosa.[9]

To date, studies on STH infections and biomarkers of gut permeability and inflammation have been mostly focused on school-aged children, while similar studies on preschool children have been limited.[10,11] Therefore we aimed to evaluate the associations between STH infection, intestinal permeability, and intestinal inflammation in preschool children in an STH-endemic area in Nangapanda District, Ende Regency, East Nusa Tenggara.

Methods

In this cross-sectional study, stool samples were obtained from children aged 12-59 months in the Nangapanda Subdistrict, Ende Regency, East Nusa Tenggara, in September 2019. East Nusa Tenggara is an STH infection-endemic area of Indonesia, and Nangapanda is one of the subdistricts with a high prevalence of these infections.[12] This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

The sample size was determined by using a formula from Charan & Biswas for cross-sectional studies.[13] The expected affected proportion in the population was taken from a previous study.[14] By random sampling, we included children aged 12-59 months and whose parents provided verbal informed consent. The age and sex of the children were obtained from a questionnaire during house-to-house visits. Parents were given labeled stool containers and instructions to collect their child's stool in the morning. Specimens were collected by the research team every morning during house-to-house visits.

Microscopic examination was carried out in the field using Kato-Katz method for intestinal worm eggs in fresh feces. The Kato-Katz method uses a plastic mold with a hole in the center, which can be filled with approximately 41.7 mg of feces previously sieved with a nylon screen. Next, the feces specimens were covered with cellophane that had been soaked in malachite-green stain. Species identification and worm egg counting was carried out by observing the morphology of the eggs under a microscope with 10x and 40x magnification. Calculation of worm eggs per gram of feces (EPG) was carried out by multiplying the observed number of eggs by 24.

The prevalence of intestinal helminth infections was computed from the number of specimens containing worm eggs of all examined stool specimens. The severity of infection with each STH species was classified according to the WHO as mild, moderate, or severe.[15]

Stool extraction was carried out on 50 mg of frozen stool specimens (without preservatives) dissolved in extraction buffer solution (*BioVendor*, Brno, Czech Republic, cat no. C005821) to obtain a dilution factor of 50x in a polypropylene tube. The solution was centrifuged to obtain a supernatant, which was then dissolved in a dilution buffer to produce a dilution factor of 200x. The diluted supernatant was used for ELISA.

FC concentrations were measured using the S100A8/A9 (calprotectin) human ELISA kit (*BioVendor*, Brno, Czech Republic) following the

manufacturer's instructions. An FC concentration of <50 mg/kg was considered normal, whereas a concentration of ≥50 mg/kg was considered elevated, as described in a previous study.[11]

A hundred milligram of frozen stool sample was dissolved in 5 mL of wash buffer. The sample solution was centrifuged at 2000 g for 10 minutes to obtain a supernatant solution, diluted with a ratio of 1:250 using 1x wash buffer. The resulting dilution of 100 μL was used in the ELISA test. The concentration of alpha-1-antitrypsin was measured using the alpha-1-antitrypsin ELISA kit (Immuchrom, Heppenheim, Germany) following the manufacturer's instructions. AAT concentrations of <0.27 mg/g were considered normal; those ≥0.27 mg/g were considered elevated.[16]

Data distribution was analyzed by Kolmogorov-Smirnov test. The concentrations of intestinal permeability biomarker (AAT) and intestinal inflammatory biomarker (FC) between the the infected and uninfected groups were compared using the Mann-Whitney test. The correlation between AAT and FC concentrations was analyzed using Spearman's correlation. The associations of helminth infection status with AAT and FC, respectively, was analyzed using the chi-square or Fisher's exact test. The same tests were employed to assess potential confounding factors by analyzing the data stratified by sex (male and female) and age group (20-29 months, 30-39 months, 40-49 months, and 50-59 months). Statistical analysis was performed using *SPSS ver. 22* (*IBM*, Armonk, New York, USA). Results with P values <0.05 were considered to be statistically significant.

Results

A total of 111 preschool children provided stool specimens for the study. **Table 1** shows the characteristics of participants. Of 111 children who provided stool specimens, the prevalence of STH infection was 17.1%. The most common species found to infect preschool children was A. lumbricoides (7.2%), followed by *T. trichiura* (6.3%), and infection with more than one species (3.6%). A. lumbricoides infection in preschool children tended to be of mild intensity (mild: 6.3% of all subjects; moderate: 4.5%), whereas in *T. trichiura* infection, only mild infection was found. The geometric mean EPG of A. lumbricoides and T. trichiura were 2,855 and 83, respectively.

Among the 111 collected stool samples, only 68 samples had sufficient quantity for both AAT and FC measurements, while 9 other samples were only sufficient for FC testing. When the concentration of fecal biomarkers was grouped based on the cutoff, 64.71% (44/68) of participants had AAT concentrations ≥0.27 mg/g, with a median 0.92 mg/g. On the other hand, 35.06% (27/77) of PSC had FC concentrations ≥50 mg/kg, with median 132.24 mg/kg. Spearman's correlation analysis revealedshowed that the biomarker of for intestinal permeability, AAT, had no significant correlation with intestinal inflammation (FC) (rho= 0.118; P= 0.339).

The median concentration of fecal biomarkers based on STH infection status can be seen in **Figure 1**. Mann-Whitney analysis revealed that there was no significant difference in AAT concentration between infected and uninfected subject groups. The AAT concentration in subjects infected with a single STH species (*A. lumbricoides* or *T. trichiura*) as well as co-infection with both species was not significantly different from the uninfected group either. Fisher's exact test showed that none of the types of infection had significantly different AAT concentrations compared to the other groups.

Table 1. Characteristics of the study population

Participant characteristics	(N=111)
Sex, n (%)	
Male	60 (54.1)
Female	51 (45.9)
Age, n (%)	
20-29 mos	38 (34.2)
30-39 mos	39 (35.1)
40-49 mos	26 (23.4)
50-59 mos	8 (7.2)
Positive STH infection status, n (%)	19 (17.1)
Number of species STH, n (%)	
A. lumbricoides only	8 (7.2)
T. trichiura only	7 (6.3)
A. lumbricoides + *T. trichiura*	4 (3.6)
STH infection intensity, n (%)	
A. lumbricoides	
Mild	7 (6.3)
Moderate	5 (4.5)
T. trichiura	
Mild	11 (9.9)

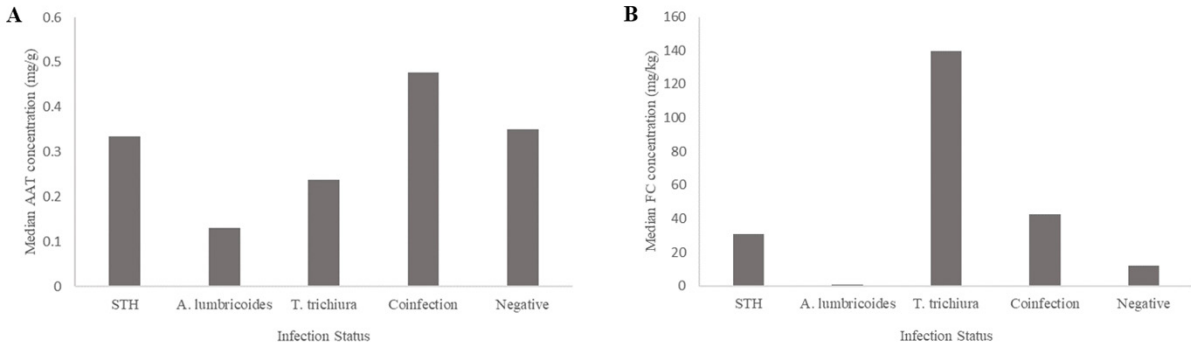

Figure 1. Median fecal biomarker concentrations based on STH infection status: (A) AAT; (B) FC

There was also no significant difference in FC concentration between the infected and uninfected groups. Subjects infected with T. trichiura had a significantly higher FC concentration than those not infected with STH (Mann-Whitney test: P=0.042). However, no significant associations difference in FC levels were found in the A. lumbricoides group or the co-infection group compared to the uninfected group. Gender and age group were also not significantly associated with AAT or FC concentrations (data not shown).

Discussion

This study showed no significant association between STH infection and AAT, a gut permeability biomarker. A previous study in Bangladesh on children under two years of age similarly found no significant association between trichuriasis and AAT.[17] In a Makassar study in school-age children, low socioeconomic status, but not intestinal parasite infection, was associated with increased intestinal permeability.[18] Another study in children under two years of age in São Tomé and Príncipe showed that a very weak association between parasite infection and AAT concentration. It is likely that AAT might be associated with other factors, such as nutritional status.[19]

The AAT concentration in our subjects tended to be above the cutoff level (≥0.27 mg/g). Further research needs to be conducted to determine the factors causing increased AAT concentration in Nangapanda District. A previous study showed that intestinal permeability can be influenced by various factors such as host genetics, co-infection with other pathogens, and lifestyle.[20]

We found that overall STH infection did not have a significantwas not significantly association associated with fecal calprotectin, the intestinal inflammatory biomarker, similar to findings of a previous study in children under two years of age.[19] However, we found that children infected with *T. trichiura,* but not *A. lumbricoides*, had a significantly higher FC concentration than uninfected children. A significant association between *T. trichiura* infection and inflammatory biomarkers was also found in the a Bangladeshi study in children under two years of age. The biomarker of intestinal inflammation used in the Bangladeshi study was neopterin, which is mainly produced by monocytes and macrophages. Infants infected with *T. trichiura* had a higher median concentration of neopterin than infants not infected with *T. trichiura*.[17] In contrast, a study of school-age children in Ecuador showed no significant correlation between *T. trichiura* infection and FC concentration. The authors also noted a tendency for *T. trichiura*-infected children to have lower FC levels than uninfected children who were not infected with T. trichiuraones.[21] The differing results from the studies in developing countries above may have been due to differences in host and parasite genetics,[22] differences in the age of the subjects, and/or history of host parasite infection.[23]

The difference in results between A. lumbricoides and *T. trichiura* infection in our study may be explained by the parasites' behavior within the host. *A. lumbricoides* has a larval migration phase in its life cycle, while *T. trichiura* does not.24 Thus, the effect of *T. trichiura* infection is more localized. The worm attaches to the host's intestinal mucosa and causes injury to the host tissue.[19] Several studies have shown the role of neutrophils in the immune response to

worms, especially when worm activity can cause injury to the tissues.[25] Histological observations of *Heligmosomoides polygrus* infection showed neutrophil infiltration around worm cysts in the intestinal tissue of mice.[26]

We found no association between AAT and FC. Previous studies have been very limited. Increased intestinal permeability resulting from barrier dysfunction is known to induce low-grade inflammation due to the translocation of microbes and other pathogens.[27] Other evidence suggests that impaired intestinal permeability alone may not be sufficient to cause inflammation. Specific proteins related to the intestinal barrier are indicated to play a role in the regulation and repair of epithelial injury.[28]

The prevalence of STH infection in our study was lower than a previous study conducted at the same location in 2014, in which the prevalence of STH infection in PSC preschool children was 58.8%.[12] Regular anthelmintics and improved hygiene practices could be reasons for the decreased prevalence of STH infection in our study. Another effect of worm control through anthelminthic treatment can be seen from the decrease in STH species diversity that infected PSC preschool children at this location, from three species (*A. lumbricoides, T. trichiura*, and hookworm) to two species (*A. lumbricoides and T. trichiura*). *A. lumbricoides* and *T. trichiura* have different transmission pathways than hookworms; the two former species infect humans through fecal-oral transmission. In contrast, infective hookworm larvae cause infection by penetration through the skin, therefore, there is a possibility that the practice of using footwear by PSC preschool children has been improved, thereby minimizing contact between the skin and potentially contaminated soil.[30] Another study showed the importance of parents'/caregivers' role in the education and supervision of hygiene practices of PSCpreschool children.[10] Another possible explanation is that albendazole effectively reduces STH, particularly hookworm and *A. lumbricoides*, but is less effective against *T. trichiura*. This result is consistent with previous research conducted in Nangapanda, which showed that the prevalence of hookworm and *A. lumbricoides* infections decreased significantly and remained low. In contrast, *T. trichiura* infection did not show a significant reduction.[31,32] The persistent *T. trichiura* infection in the community, despite repeated anthelminthic administrations, may have contributed to the positive association with FC, the inflammatory marker. Therefore, a longitudinal study with effective antheminthics against *T. trichiura* would be needed to clarify the potential role of *T. trichiura*.

This study had several limitations, including the low number of subjects testing positive for STH infection, which might have affected the results and interpretation of the statistical analysis.[33] In addition, most of the STH infections in our population were mild. Furthermore, in populations with mild STH infection intensity, microscopic examination using the Kato-Katz method to determine the prevalence and intensity of STH infection is considered less sensitive compared to other STH diagnostic methods, especially molecular-based diagnostic methods.[34]

In conclusion, STH infection did not have a significant association with fecal biomarkers, except between *T. trichiura* infection status and increased FC. The fact that the majority of PSC preschool children in this area had increased levels of AAT, the intestinal permeability marker suggests that other factors besides STH infection need to be investigated further for their impact on the pre-school children's health.

Conflict of interest

None declared.

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