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2015

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de Gier, B. (2015). *Helminth infections and micronutrients in children*.

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CHAPTER 3

Species-specific associations between soil-transmitted helminths and micronutrients in Vietnamese schoolchildren

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Provisionally accepted, American Journal of Tropical Medicine and Hygiene

Abstract

Soil-transmitted helminth infections and micronutrient deficiencies are closely related and often co-exist among low income populations. Here, we studied the association between infections with specific STH species and micronutrient status in rural Vietnamese schoolchildren. Children (n=510) aged 6-9 years were recruited from two primary schools. STH infections were determined in stool samples. Hemoglobin, ferritin, retinol and zinc were measured in blood samples, as well as CRP to control for inflammation. Iodine excretion was measured in urine. Associations of single and multiple infections with *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm with micronutrient status (blood hemoglobin, plasma ferritin, retinol, and zinc and urinary iodine) were estimated by regression techniques. *Ascaris* infections showed a specific and dose-dependent negative association with vitamin A. *Trichuris* and hookworm infections were associated with lower hemoglobin concentration, but not with plasma ferritin. *Trichuris*-infected children had zinc-deficiency less often than uninfected children. In conclusion, our study shows species-specific associations between STH infections and micronutrient status in children. The different life cycles of STH species might have specific effects on the absorption or loss of specific micronutrients. Tailor-made combinations of deworming and nutritional interventions may be needed to improve child health and nutrition.

Introduction

Soil-transmitted helminths (STH) *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm and micronutrient deficiencies such as iron, zinc and vitamin A pose major health issues in the developing world. Both STH infections and micronutrient deficiencies are highly prevalent in tropical countries and are strongly related to poverty^{1,2}. As school-age children are most often infected with STH and micronutrients are essential for growth and development, these children are particularly vulnerable to both conditions.

Various studies have reported associations between STH infections and micronutrient status in children^{3,4}. However, the reported associations differed between studies performed in different populations, harboring different STH species and measuring different markers of micronutrient status⁵. While STH species are often studied as a group, they represent distinct organisms with different life cycles and transmission patterns. Adult *Ascaris lumbricoides* worms reside in the jejunum. They are the largest of the STH species, reaching up to 40 cm in length, and can obstruct the gut lumen in high-intensity infection¹. *Ascaris* feeds on intestinal content, not on host tissue⁶. *Trichuris trichiura* inhabits the colon and feeds on the gut mucosa. Hookworm feeds on host blood in the upper small intestine and is therefore often indicated as an important cause of anemia⁶. As the different STHs inhabit different parts of the gut and employ distinct feeding mechanisms they may have specific effects on absorption or loss of certain micronutrients. In addition, the extent of this effect may be dependent on the infection intensities of these intestinal worms. Using baseline data from a micronutrient fortification and deworming trial in rural Vietnamese schoolchildren, we aimed to study species-specific associations of STH infections with iron, hemoglobin, vitamin A, zinc and iodine status.

Methods

Study population

A random selection of 510 children aged 6-9 was recruited from two primary schools in Hung Yen province in Northern Vietnam. Baseline data were collected in January 2007. Exclusion criteria were severe malnutrition, obesity, hemoglobin concentration below 80 g/L (referred to health center) chronic illness, congenital abnormalities, mental or severe physical handicap or having received deworming treatment in the last 6 months. Written informed consent was obtained from parents or caregivers. Ethical approval was obtained from the Ethical Committee on Human Research of the National Institute of Nutrition (NIN), Hanoi, Vietnam, and the Human Ethics Committee of Mahidol University, Bangkok, Thailand. This study population has been described in detail elsewhere⁷.

Measurements

Demographic characteristics such as age and sex were determined by interviewing parents or caregivers of the children by trained research assistants. STH infections were determined in stool samples by Kato-Katz (duplicate 25 mg smears of one stool) at the Medicine Laboratory Technology co. Ltd, Hanoi, Vietnam and expressed as eggs per gram stool. Hemoglobin concentrations were measured in a 2 mL nonfasting blood sample, drawn in an EDTA vacutainer, by an electronic Coulter counter at the Medicine Laboratory Technology co. For biochemical measurements of micronutrients, 4mL blood samples were drawn in a heparinized trace element-free tube. Plasma ferritin concentration was measured by ELISA according to the kit manufacturer's protocol (Ramco Laboratories) at the National Institute of Nutrition. Plasma retinol concentration was determined by reverse-phase HPLC (LC-10 ADVP) and plasma zinc was analyzed using a flame atomic absorption spectrophotometer (GBC, Avanta+) using trace element-free procedures at NIN. Results were verified against reference materials for zinc (Merck) and iodine (BDH Laboratory Supplies). Plasma CRP was measured by ELISA according to the kit manufacturer's protocol (Diagnostic Systems Laboratories). Iodine concentration was measured in urine samples, using spectrophotometric methods and was performed at the Provincial Preventive Medicine Center, Thai Nguyen, Vietnam. For quality control, ten percent of samples were measured in duplicate for each biochemical parameter. The within-assay variability was <6% for all parameters and between-assay variability was <10%.

Definitions

STH infection intensities were categorized according to WHO references⁶. *Ascaris* infections with <5.000 eggs/gram feces (epg) were categorized as light, 5.000-50.000 epg as moderate and >50.000 epg as heavy. *Trichuris* infections below 1.000 epg were categorized as light, 1.000-10.000 epg as moderate and > 10.000 as heavy. Hookworm infections below 2.000 epg were defined as light, 2.000-4.000 epg as moderate and >4.000 epg as heavy. Vitamin A deficiency was defined as plasma retinol below 0.70 $\mu\text{mol/L}$, marginal vitamin A status was defined as retinol below 1.05 $\mu\text{mol/L}$ ⁸. Iron deficiency was defined as plasma ferritin below 15 $\mu\text{g/L}$ and anemia as hemoglobin below 115 g/L ⁹. Zinc deficiency was defined as plasma zinc <9.9 $\mu\text{mol/L}$ and low urinary iodine excretion was defined as <100 $\mu\text{g/L}$ ^{10,11}. CRP was considered elevated when concentrations exceeded 5 mg/L ¹².

Statistical analysis

Statistical analyses were done using SPSS version 21 (IBM, New York, USA). Double and triple infections were combined into a 'multiple STH infections' group. Single and multiple infections were compared to the uninfected group in all analyses. Associations with micronutrient concentrations were estimated by linear regression with the micronutrient concentration as dependent variable. Variables ferritin and iodine were log-transformed to achieve a Gaussian distribution. Associations with deficiencies of micronutrients (as dichotomous outcome) were analyzed by logistic regression. For estimations of associations between infection intensities and micronutrient status, intensities (light, moderate and heavy) were analyzed as categorical independent variables. In all regression analyses, the primary independent variable STH infection was accompanied by covariates sex, age (in months) and elevated CRP (yes/no). Interaction between two STH species was studied by adding interaction terms to the full model including the two separate species. Statistical significance was defined as $p < 0.05$, whereas an interaction was regarded as significant if $p < 0.10$.

Results

The STH infection prevalence was high (80.2%) in this study population (Table 1). *Ascaris lumbricoides* was the most common STH species (64.1%), followed by *Trichuris trichiura* (53.7%) and hookworm (5.3%). While *Trichuris* and hookworm infection intensities were generally light, most *Ascaris* infections were of moderate intensity. Figure 1 shows the distribution of single, double and triple STH infections among the Vietnamese schoolchildren. In this study population, children were most often found to be infected by both *Ascaris* and *Trichuris* (N=197, 38.6%).

Table 3.1. Characteristics of the study population

	n (%)
N	510
Male	243 (47.6%)
Age¹	7.5 ± 0.9
Any STH infection	409 (80.2%)
<i>Ascaris lumbricoides</i>	327 (64.1%)
Light (<5.000 epg)	116 (22.7%)
Moderate (5.000-50.000 epg)	198 (38.8%)
Heavy (>50.000 epg)	13 (2.5%)
<i>Trichuris trichiura</i>	274 (53.7%)
Light (<1.000 epg)	241 (47.3%)
Moderate (1.000-10.000 epg)	33 (6.5%)
Heavy (>10.000 epg)	0 (0.0%)
Hookworm	27 (5.3%)
Light (<2.000 epg)	25 (4.9%)
Moderate (2.000-4.000 epg)	2 (0.4%)
Heavy (>4.000 epg)	0 (0.0%)
CRP > 5mg/L	78 (16.7%)

¹: mean ± sd

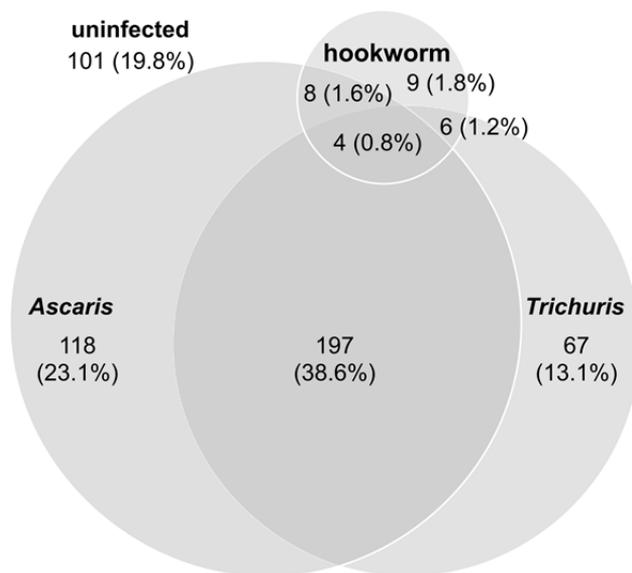


Figure 3.1. Distribution of single, double and triple STH infections among the 510 Vietnamese schoolchildren in this study population

The study population's micronutrient status (concentrations as well as prevalences of deficiency and marginal status) by STH infection is shown in Table 3.2. *Ascaris* single infections were significantly associated with lower plasma retinol (aB -0.10 $\mu\text{mol/L}$, 95% CI -0.17;-0.02) and higher prevalence of marginal vitamin A status (aOR 2.31, 95% CI 1.23; 4.31). Vitamin A deficiency occurred almost exclusively in *Ascaris*-infected children; only 2 out of 52 vitamin A deficient children did not harbor an *Ascaris* infection. Multiple infections were also significantly associated with all three measures of vitamin A status. This was most likely attributable to the *Ascaris* infection, as most cases of multiple infections included *Ascaris* and there was no significant interaction effect on plasma retinol between *Ascaris* and *Trichuris* (aB -0.03 $\mu\text{mol/L}$, p 0.51) or *Ascaris* and hookworm (aB -0.00 $\mu\text{mol/L}$, p 0.98).

Table 3.2. Micronutrient concentrations and prevalence of (marginal) micronutrient deficiencies among uninfected children and children with single and multiple STH infections, respectively.

	STH uninfected n (%)	<i>Ascaris</i> single infection n (%)	<i>Trichuris</i> single infection n (%)	Hookworm single infection n (%)	Multiple STH infections n (%)
N	101	118	67	9	215
Retinol $\mu\text{mol/L}^1$	1.13 \pm 0.21	1.03 \pm 0.30*	1.13 \pm 0.2	1.08 \pm 0.13	0.98 \pm 0.26*
Marginal vitamin A status (<1.05 $\mu\text{mol/L}$)	28 (34.1)	60 (56.6)*	21 (33.3)	1 (11.1)	128 (61.5)*
Vitamin A deficiency (<0.70 $\mu\text{mol/L}$)	1 (1.2)	17 (16.0)*	0 (0.0)	0 (0.0)	34 (16.3)*
Zinc $\mu\text{mol/L}^1$	8.30 \pm 1.93	8.53 \pm 2.14	8.71 \pm 2.36	8.45 \pm 2.60	8.67 \pm 2.19
Zinc deficiency (<9.9 $\mu\text{mol/L}$)	70 (86.4)	79 (75.2)	46 (73.0)*	6 (66.7)	159 (76.8)
Hemoglobin g/L^1	122.00 \pm 5.87	121.08 \pm 7.32	116.88 \pm 7.51*	117.44 \pm 8.41*	118.13 \pm 7.67*
Anemia (Hb < 115 g/L)	12 (11.9)	14 (11.9)	30 (44.8)*	3 (33.3)	68 (31.6)*
Ferritin ($\mu\text{g/L}$)²	61.68 (43.09-82.73)	63.99 (41.37-88.09)	59.89 (47.00-75.48)	69.21 (48.00-86.55)	65.11 (42.53-84.38)
Iron deficiency (ferritin <15 $\mu\text{g/L}$)	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	1 (0.5)
Urinary iodine $\mu\text{g/L}^2$	108 (77.00-167.00)	112.50 (79-149)	106 (83.00-174.00)	96.00 (77.00-255.00)	115.00 (77.00-167.00)
Low urinary iodine excretion (<100 $\mu\text{g/L}$)	46 (45.5)	50 (42.4)	27 (40.3)	5 (55.6)	91 (42.3)

* significantly different from uninfected ($p < 0.05$)¹: mean \pm sd²: median (IQR)

Plasma zinc concentrations tended to be higher in children with STH infection than in those without. Zinc deficiency was found to be negatively associated with *Trichuris* infection (aOR 0.39, 95% CI 0.16-0.94), although the associations of zinc deficiency with *Ascaris* and multiple infections were also borderline significant (aOR 0.46, 95% CI 0.21;1.01 and aOR 0.49, 95% CI 0.24; 1.01, respectively).

Hemoglobin concentrations were significantly lower in children with *Trichuris* (aB -5.32 g/L, 95% CI -7.46;-3.17), hookworm (aB -6.42 g/L, 95% CI -11.20; -1.64) and multiple infections (aB -4.20 g/L, 95% CI -6.02; -2.37) than in those uninfected. No interaction effect was observed between *Trichuris* and hookworm infections on hemoglobin (aB 2.72 g/L, p 0.36). Anemia occurred significantly more often in children with *Trichuris* (aOR 11.74, 95% CI 4.17;33.04) and multiple (aOR 4.91, 95% CI 2.11; 11.39) infections. However, none of the STH infections were associated with iron status as measured by plasma ferritin concentrations. No associations between urinary iodine excretion and STH infections were observed.

Ascaris infection intensity showed a dose-dependent association with plasma retinol concentrations (aB -0.08 $\mu\text{mol/L}$, 95% CI -0.1; -0.06) and with the prevalence of marginal vitamin A status (Wald 26.06, $p < 0.001$) (Figure 3.2). The same relationship was found for vitamin A deficiency (Wald 30.34, $p < 0.001$) (Figure 3.2). No intensity-dependent relationships were found for *Trichuris* or hookworm infections and hemoglobin concentration or for *Trichuris* infection and zinc deficiency.

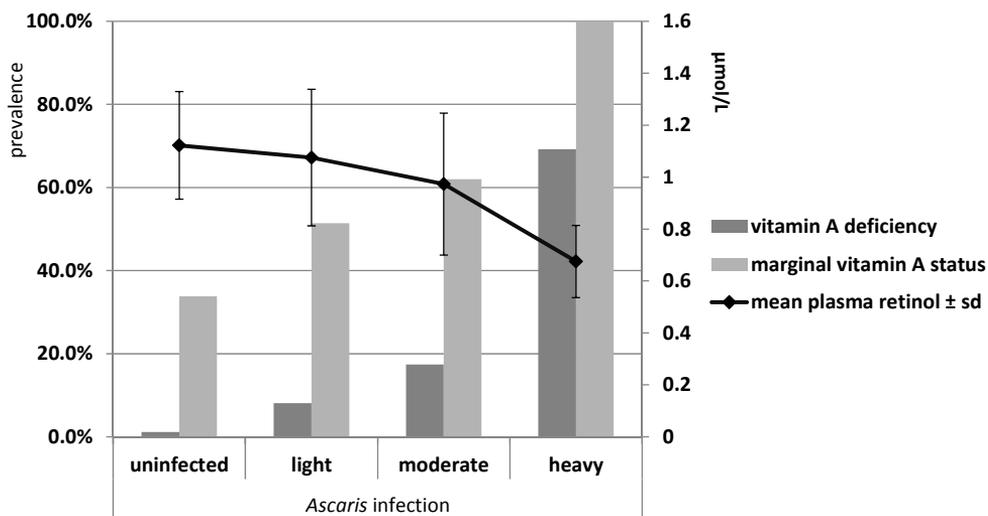


Figure 3.2. Mean plasma retinol and prevalences of marginal and deficient vitamin A status across *Ascaris* infection intensity categories.

Discussion

This study in rural Vietnamese schoolchildren shows that associations between STH infections and micronutrient status are STH species specific. *Ascaris* single infections and multiple infections were significantly associated with lower retinol concentrations. *Ascaris* infection intensity showed an intensity-dependent relationship with plasma retinol and with prevalences of marginal vitamin A status and vitamin A deficiency.

Associations have been reported between *Ascaris* and xerophthalmia (dry eyes), a consequence of vitamin A deficiency^{13,14}. However, epidemiological studies addressing associations between *Ascaris* infection and vitamin A (retinol) itself have shown conflicting results¹⁵⁻²⁰. A recent study conducted in Kenya reported higher prevalence of vitamin A deficiency (defined as low retinol-binding protein) in *Ascaris*-infected pre-school children. In accordance with our findings, moderate intensity infections had a stronger association with vitamin A deficiency than light infections did²¹.

While we cannot infer causality from our cross-sectional data, we speculate that *Ascaris* infection might impair vitamin A absorption from the diet. Vitamin A is absorbed after emulsification with fatty acids and bile salts in the jejunum²². *Ascaris* may interfere with this process as the adult worms reside in and can obstruct the jejunum. If so, this interference with absorption may extend to other fat-soluble vitamins D, E and K. In the 1970s, small clinical studies have reported negative effects of *Ascaris* infection on fat and vitamin A absorption^{23,24}. However, a 1993 study could not confirm this theory²⁵. In addition, vitamin A deficiency may predispose to *Ascaris* infection by impairing gut mucosal immunity and integrity^{26,27}. However, this would increase susceptibility to STH infections in general, not specifically to *Ascaris*. An observational prospective study in Panama reported less *Ascaris* reinfection in children receiving vitamin A supplements²⁸. However, two randomized placebo-controlled trials found no protective effect of vitamin A supplementation on *Ascaris* infection^{29,30}. In the children in the present study, biscuits fortified with multiple micronutrients including vitamin A resulted in a lower *Ascaris* re-infection rate⁷.

Hemoglobin concentrations were lower in *Trichuris*, hookworm, and multiply-infected children than in those uninfected. Surprisingly, these infections were not associated with ferritin concentrations. Plasma ferritin reflects the amount of intracellular iron stores. During inflammation, iron is redistributed in the body by intracellular sequestering, reducing its availability to pathogens. This phenomenon has been termed nutritional immunity, as it can reduce susceptibility to infections³¹. In the present study, only CRP was available as indicator for inflammatory status, perhaps leading to incomplete adjustment of ferritin concentrations during inflammation. Ideally alpha-1-acid glycoprotein (AGP)

concentration should have been included as well. Ferritin can still be increased in the convalescent phase of the acute phase response after CRP concentrations have already decreased, while AGP is still elevated³². Alternatively, the observed anemia may not have been due to iron deficiency but a deficiency in folate or vitamin B12, which were not measured in this study³³.

The observed positive association between zinc and STH infections was surprising. Like vitamin A, zinc is absorbed in the jejunum. As *Trichuris* and hookworm are found lower in the gastrointestinal tract, these species might not interfere with zinc absorption. Still this does not explain higher zinc concentrations in infected children. Zinc concentrations are affected by inflammation also, with lower zinc concentrations during the acute phase response¹². Perhaps the helminths have given rise to anti-inflammatory responses, leading to higher zinc concentrations in the infected children³⁴. As with our ferritin results, we were not able to completely adjust for inflammation because AGP data was not available¹².

Our study has strengths and limitations. All three common STH infections were prevalent in this population, which meant the number of children with single infections by either *Ascaris* or *Trichuris* and with multiple infections were large enough to provide reasonable estimates for these groups separately. Also, the presence of different infection intensities, especially for *Ascaris*, allowed us to study dose-response relationships and may render our results more generalizable than studies with only light infection intensities or clinical cases. A limitation is the absence of AGP measurements, which would have allowed for better adjustment of micronutrient measurements for inflammation¹².

In conclusion, our study demonstrates STH species-specific associations with micronutrient status in schoolchildren. Moreover, this association was clearly related to infection intensity for *Ascaris* and vitamin A status. Hence, both prevalence and intensity of specific helminth infection species in a population may predispose to specific nutritional deficiencies. If so, then some micronutrient deficiencies, such as vitamin A deficiency, are best combated by a combination of deworming and nutritional interventions. Tailor-made public health strategies according to the STH species and micronutrient deficiencies present in a specific population may need to be designed in order to improve child health and nutrition in the most effective way.

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