

GENDER DIFFERENCES IN GROWTH OF SCHOOL-AGED CHILDREN WITH SCHISTOSOMIASIS AND GEOHELMINTH INFECTION

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Abstract. Light or moderate intensity infection with *Schistosoma mansoni* may contribute to growth deficits. We report on the effects of treatment for *S. mansoni* on growth and development in Brazilian schoolchildren. Anthropometric measurements were taken from 539 *S. mansoni*-infected children and their age- and sex-matched egg-negative controls between the ages of 7 and 15 years. The children as a whole exhibited chronic malnutrition, with growth retardation in height evident in 21% of the population. Infected children, however, were significantly smaller in height, weight, mid upper arm circumference (UAC), tricep skinfold (TSF), and subscapular skinfold (SSF) measurements than control children ($P < 0.05$). These differences were due primarily to a greater disparity between infected and egg-negative girls in height ($P < 0.01$), weight ($P = 0.01$), UAC ($P = 0.02$), and TSF ($P < 0.01$). Nevertheless, girls demonstrated a better level of development and nutrition compared with boys. While infected boys were shorter and weighed less than controls, these differences were not significant. Growth and development in girls was negatively correlated with intensity of infection. Coinfection with *S. mansoni* and *Trichuris* appeared to act synergistically in the development of malnutrition.

Children between the ages of 5 and 15 years often represent 50% of the population in developing countries; thus, their level of nutrition and health has a substantial impact on a community. Despite a lower incidence of diarrheal and respiratory diseases, nutritional status in school-aged children worsens with age. While factors affecting the growth and development of preschool children are well-documented, the factors influencing the growth of school-aged children are not as clear. One of the factors emphasized in The World Development Report 1993 is the relationship between parasitic infection and malnutrition.¹ Schistosomiasis is one of the most widespread and morbid of chronic parasitic diseases. An estimated 200 million people are infected, and infection is most intense in children 5-15 years of age.² A hepatic form of this disease, caused by the species *Schistosoma mansoni*, results from the host's immunologic reaction to parasite eggs deposited in the liver. Drugs to treat schistosomiasis are now safe and highly effective³ so that several countries, including Brazil, have instituted campaigns of periodic treatment involving large portions of the infected population. Mass chemotherapy has not eliminated the disease, since children readily become reinfected, but it has greatly reduced the prevalence and intensity of infection. The result has been to increase the the proportion of moderate- and low-intensity infections.

In general, the most heavily infected people show evidence of hepatosplenomegaly and portal hypertension. Morbidity has been traditionally considered a result of only severe schistosome infections; persons with light infections were thought to suffer no ill effects. Therefore, some control strategies have focused only on reducing of the number of heavily infected individuals. There is increasing evidence, however, that even low or moderate intensity infection significantly retards childhood growth and development.⁴⁻⁶ Since more than 90% of those infected have modest parasite burdens, it is important to carefully assess the impact of these intensities of infection on overall health.

Schistosome infections are rarely the only chronic infection of children in a community. *Ascaris lumbricoides* and *Trichuris trichiura* are extremely common parasites referred to together as geohelminths. These parasites are transmitted by ingestion of soil contaminated with feces containing the parasites' eggs. In many areas of the world, infection with geohelminths may be considered universal. Overt disease can only rarely be attributed to *Ascaris* or *Trichuris*, but they have been associated with malnutrition in children.¹

The primary purpose of this study was to determine whether the association between schistosome infections and nutritional status extends to a population that has received prior mass treatment for schistosomiasis and to examine the epidemiologic profile of that community for any distinguishing characteristics associated with growth deficits. We report on the baseline anthropometric measurements of a two-year prospective, placebo-controlled, double-blinded study on the impact of light and moderate *S. mansoni* infection on the nutritional status of school-aged children in Brazil.

METHODS

Population and anthropometrics. A community with a population of 25,000 was selected in the state of Bahia, Brazil. The study site is a rural town (Nazare das Farinhas) located approximately 100 km from the state capital and 40 km from the Atlantic Ocean. For 200 years, it served as a commercial center for transshipping agricultural products (e.g., manioc and bananas) brought from farms in the surrounding districts. The city also contains a brick factory and a manufacturing plant for processing palm oil used in cooking in this region of Brazil. A large river divides the city and drains multiple streams and low lying swampy areas within the city. The river also receives the effluent from the city's sewers. From the 1991 Federal Census, the total urban and rural population is 25,000, and 60% of the population is between the ages of 6 and 15 years. This community last received mass chemotherapy with oxamniquine for schisto-

somiasis in 1988 when the prevalence of infection in the community as a whole was approximately 30%. The data for this study were collected in 1992. Seventeen of the 21 public schools were included and all students 7–15 years of age at these schools were given receptacles and asked for a stool sample. The stool examinations were performed using the quantitative Kato-Katz method.⁷ Students whose first stool was positive for *S. mansoni* eggs were asked for two more samples to better determine intensity of infection. Children whose first stool sample was negative for schistosome eggs served as controls for baseline data. The terms egg-negative and controls are used interchangeably for this group. The presence of eggs of *Ascaris* and *Trichuris*, the most common intestinal helminths, was also recorded.

Anthropometric measurements were taken in accordance with the methods of Weiner and Lourie,⁸ with the exception that arm measurements were made on the right arm rather than the left, since reference data⁹ are based on the right arm. The National Center for Health Statistics (Hyattsville, MD) anthropometric charts for the evaluation of body composition provide information on skinfold thicknesses, body circumference, and body proportions of U.S. children.⁹ The measurements to assess growth were height and weight, and to assess body composition were mid upper arm circumference (UAC) and tricep skinfold (TSF) and subscapular skinfold (SSF). Weights were obtained using Filizola ID-1500 digital battery/electric operated scales read in 0.1-kg increments (Industria Filizola S/A, Sao Paulo, Brazil). Heights were measured using a Ross Laboratories (Columbus, OH) stadiometer with an attached headboard. Lange skinfold calipers (Beta Technology, Inc., Cambridge, MA) were used to measure skinfold thickness. Measurements were taken twice and averaged.

Anthropometric evaluation, like other techniques, is subject to error in data collection. Therefore, the precision (reproducibility) and accuracy of examiner measurements must be determined.^{10,11} Standardization procedures were used as an indicator of when interexaminer and intra-examiner performance had reached a satisfactory degree of precision and data collection could begin. Standardization procedures were also conducted at the end of the study to ascertain the degree of precision that had been maintained throughout the data collection period. Standardization was accomplished by having each examiner make two sets of measurements on 10 nonstudy children. The examiner made the second set of measurements while blind as to the result from the first and after a sufficient lapse of time so that their second measurement was not influenced by the first. These two sets of measurements were compared for reproducibility. For accuracy, the measurements of the examiners were compared against the measurements of the first author, whose results were used as a reference. The precision of measurement ranged from 80% (TSF) to 100% (weight) prior to data collection and 80% (TSF) to 98% (UAC) at the end of data collection. Interexaminer accuracy showed high correlations both prior to (range: $r = 0.94$ – 1.00) and following (range: $r = 0.80$ – 1.00) data collection.

Data analysis. All statistical analyses were performed with SPSS-PC+ for the IBM, Version 2.0 (SPSS, Inc., Chicago, IL). A P value < 0.05 was used to determine statistical significance in all analyses. Weight-for-age and height-for-

age z-scores were calculated using the Epi Info, Version 5.01 with Anthropometric Software Package (USD, Inc., Stone Mountain, GA). Five children in the study population were below the range of heights and weights of the reference population. Therefore, weight-for-age and height-for-age z-scores could not be calculated. The z-scores for weight-for-height were created by using tables compiled by Frisancho.¹² Weight-for-height z-scores were available for 871 children who fell within the height, weight, and age parameters of the reference population. The study data are compared with the distribution of heights and weights in a reference population of well-nourished children. The reference population established by the United States Center for Health Statistics⁹ is the recommended data set of the World Health Organization (WHO) (Geneva, Switzerland)¹⁰ and is used in this study. Anthropometric data were grouped by infection status, tested for normality, and normalized as necessary.

Stepwise regression analyses were used to describe the relationship between raw measurements and anthropometric indices of nutritional status and age. To control for any effects of gender, an indicator variable was created with gender, which was entered first on the regression equation. Analyses of covariance ([ANCOVAs] controlling for age and age² as necessary) were used to test for statistically significant differences between anthropometrics of boys and girls. Gender was significantly ($P < 0.05$) associated with all anthropometrics except height and weight-for-height z-scores, and therefore, the sexes were separated for further analyses. The chi-square test was used to compare categorical data. Sex-specific ANCOVA, controlling for age (using age or age²), were performed to compare the age-adjusted means of anthropometrics. Sociodemographics, infection status, and parasites were treated as categorical variables in the ANCOVAs.

Sociodemographic index. To help determine whether sociodemographic factors influenced patterns of growth observed between infected and egg-negative schoolchildren, interviews were conducted in the homes of 34% of the study population selected at random by the students' serial number. The interviews were conducted by the three investigators trained in nutritional anthropology (AMOA, MSP, and IMP). Three hundred fifty-three interviews were completed, representing all of the selected households. The results of questions and interviewer observations were recorded and grouped into quality of life and sociodemographic categories. Variables that originally were described at more than three levels were compressed to either two or three levels. These composite indices were compared using chi-square analysis for differences between infected and egg-negative groups.

RESULTS

Population characteristics. A total of 539 *S. mansoni*-infected children and 508 sex- and age-matched, schistosome egg-negative controls were measured for growth and body composition. There were no statistically significant differences in the number of boys and girls within or between the infected and egg-negative groups, nor was the mean age of each group different (Table 1).

Comparing the infected children with matched controls,

TABLE 1
Selected characteristics of school children in Nazare, Brazil

Characteristic	<i>Schistosoma mansoni</i> -infected (n = 539)		Egg-negative (n = 508)	
Sex				
Boys	48.1%		46.3%	
Girls	51.9%		53.7%	
Age (months), mean SD	134.53	23.20	134.03	22.71
Anthropometrics (mean SEM)				
Weight (kg)	29.31	0.43*	30.26	0.42
Height (cm)	136.72	0.76*	138.27	0.74
Weight/age z-score	-1.15	0.04*	-0.97	0.04
Height/age z-score	-1.26	0.05*	-1.00	0.05
Weight/height z-score	0.46	0.03	0.48	0.03
Arm circumference (cm)	18.91	0.23*	19.20	0.21
Tricep skinfold (mm)	7.05	0.34*	7.58	0.32
Subscapular skinfold (mm)	5.33	0.24*	5.51	0.23
Quality of life	%†		%	
House construction				
Walls				
Adobe	64.7		66.2	
Brick	35.4		33.8	
Floor				
Tile	17.4		17.8	
Cement	67.4		69.4	
Dirt	15.2		12.7	
Electricity	95.7		99.4	
Toilet	78.8		78.3	
Municipal water	49.5		55.4	
Municipal sewer	25.0		28.0	
Gas stove	90.8		93.0	
Refrigerator	61.4		63.1	
Radio	27.6		27.6	
TV	23.2		22.6	

* Mean age-adjusted measurement is significantly less ($P \leq 0.05$) than for controls.

† Result of survey of 34% of households. Schistosome-infected, n = 184; egg-negative, n = 157.

there were statistical differences in two of the indices of sociodemographic status (Table 2). The family size of schistosome-infected children was significantly larger ($P = 0.01$) and the level of maternal education was lower ($P = 0.01$) than in egg-negative children. The data indicate a slightly lower sociodemographic status for those infected with *S. mansoni*. Analysis of these sociodemographic indices to determine if they were independently associated with growth or body composition by one-way ANCOVA revealed no correlation between differences in any of these indices and anthropometric measurements.

Parasitology. At least one stool sample was obtained from 1,864 students (1,004 girls and 860 boys) and 671 (36%) were found to be infected on the first stool examination (342 girls and 329 boys). Of those positive for schistosome eggs on the initial examination, 63% provided a second stool and 28% a third. The profile of infection intensity was typical for an area where schistosomiasis is endemic and there had been mass chemotherapy four years earlier (Figure 1). Eighty percent of all infections had less than 200 eggs/gram of stool (light), 18% between 201 and 400 eggs/gram (moderate), and only 2% had greater than 400 (heavy). The limits for categories of light, moderate, and heavy infection based on stool egg counts have been shown to correlate with clinical status in Africa.¹³ These limits for intensity of infection also seem validated by anthropometric measurements in this study. In terms of other helminthic

infections, a single stool sample revealed eggs of *Ascaris* or *Trichuris* in nearly 80% of those examined (Table 3). *Trichuris* infection was significantly associated with *S. mansoni* infection, but *Ascaris* was not. There is no malaria or visceral leishmaniasis in the area, and Chagas' disease is rare.

Schistosome infection and nutritional status. Anthropometric measurements were taken on 539 *S. mansoni*-infected and 508 sex- and age-matched egg-negative controls. The nutritional status of the combined sample was poor relative to the National Center for Health Statistics reference population.¹⁴ Using WHO criteria,¹⁰ 21% of the children had low height-for-age z-scores, and 13% had low weight-for-age z-scores compared with 2.3% for the reference population. Only 0.29% had low weight-for-height z-scores, and age did not explain any significant variations. This indicates that there is predominantly linear stunting in these children due to chronic malnutrition, since the children's low weight is appropriate for their small stature. Whereas all raw measurements increased with age, weight-for-age and -height for age z-scores were negatively correlated ($P < 0.05$) with age in both the infected and control groups. Therefore, nutritional indices continue to worsen for the study population relative to the reference group as the children get older.

Children infected with *S. mansoni* were significantly more malnourished than control children in all anthropometric parameters (Table 1). When the groups were stratified by gender, all of the anthropometric differences between infected

TABLE 2
Sociodemographics of school children in Nazare, Brazil

Sociodemographic feature	<i>Schistosoma mansoni</i> -infected %*	Egg-negative %
Number in household		
≤7	65.8	79.0
≥8	34.2†	21.0
Female head of household	29.3	22.9
Mother's education		
No schooling	39.7	31.8
Primary school	44.0	38.2
Post-primary school	16.3†	29.9
Mother employed	34.8	34.4
Mother's occupation		
Government employee or merchant	31.1	32.1
Maid‡, seamstress, and fisherwoman	68.9	67.9
Father's education§		
No schooling	36.9	33.1
Primary school	47.7	46.3
Post-primary school	15.4	15.9
Father employed	76.9	60.5
Father's occupation		
Government employee or merchant	18.0	23.2
Laborer¶, guard, butcher, and fisherman	82.0	76.9

* Result of survey of 34% of households. Schistosome-infected, n = 184; egg-negative, n = 157.

† P = 0.01.

‡ Includes laundresses and odd jobs.

§ From homes of schistosome-infected children, n = 130; from homes of egg-negative children, n = 121.

¶ Includes factory and construction workers, mechanics, and odd jobs.

and egg-negative girls remained significant ($P \leq 0.02$), except for SSF (Figures 2 and 3). For boys, only SSF was significantly negatively associated with schistosome infection. The distribution of boys and girls within each category of infection (Table 3) was not significantly different ($P = 0.74$, $\chi^2 = 1.2$). Therefore, the gender-based differences in nutritional status were not due to differences in intensity of infection.

In addition to gender, the sample was further stratified by

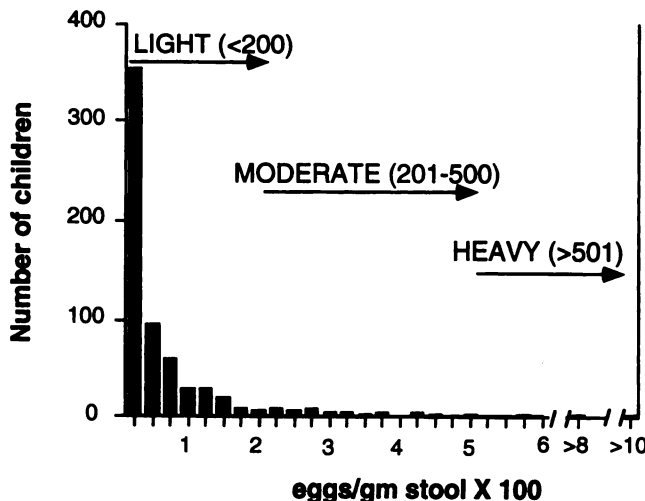


FIGURE 1. Frequency of initial egg counts and the range of infection intensities.

TABLE 3
Gender-specific intensities of infection in school children in Nazare, Brazil

Gender	Egg-negative % (n)	Intensity of infection*		
		Light % (n)	Moderate % (n)	Heavy % (n)
Boys	47.6 (235)	34.0 (168)	14.0 (69)	4.5 (22)
Girls	49.6 (273)	33.6 (186)	11.9 (66)	5.1 (28)

* Light = <200 eggs/gram of stool; moderate = 201-400; heavy = >400.

intensity of infection to determine whether differences were due only to the heavily infected group. For girls, the differences between any intensity of infection and the egg-negative group were significant. As shown in Figure 2, weight and height were significantly greater for egg-negative girls ($P \leq 0.01$) compared with girls lightly, moderately, or heavily infected with *S. mansoni*. Comparing body composition measurements (Figure 3), infected girls regardless of intensity of infection had significantly smaller UAC and TSF measurements than egg-negative girls ($P < 0.01$).

Boys, on average, suffered significantly greater deficits than girls in all measures of growth and body composition. Since girls experience the adolescent growth spurt earlier than boys, this difference in apparent nutritional status might have represented normal developmental processes in the population. Gender-based differences, however, were confirmed by age-adjusted z-scores comparing the Nazare population to the reference population. The relative disparity in nutrition using z-scores also confirmed that boys were significantly more malnourished than girls regardless of infec-

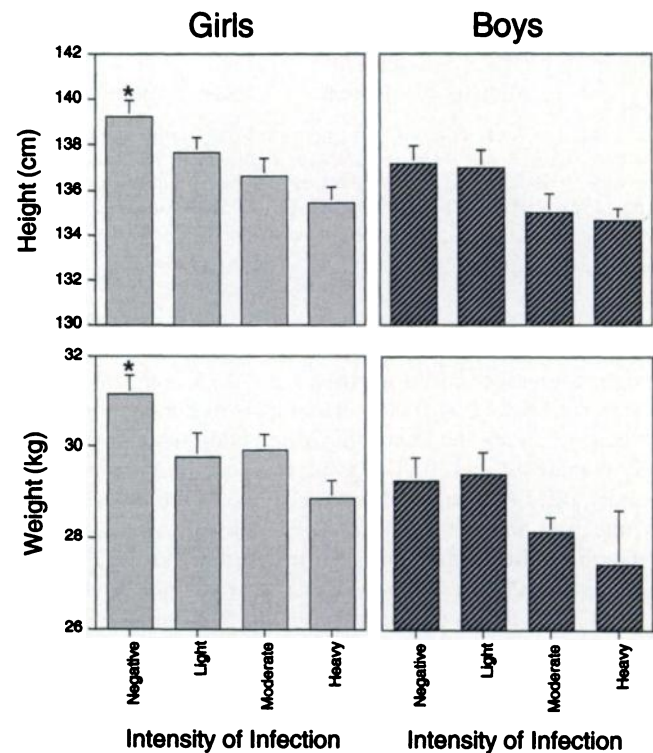


FIGURE 2. Height and weight (mean \pm SEM) compared by gender and *Schistosoma mansoni* infection status using analysis of covariance. * indicates a mean measurement that is significantly different from all intensities of infection ($P < 0.05$).

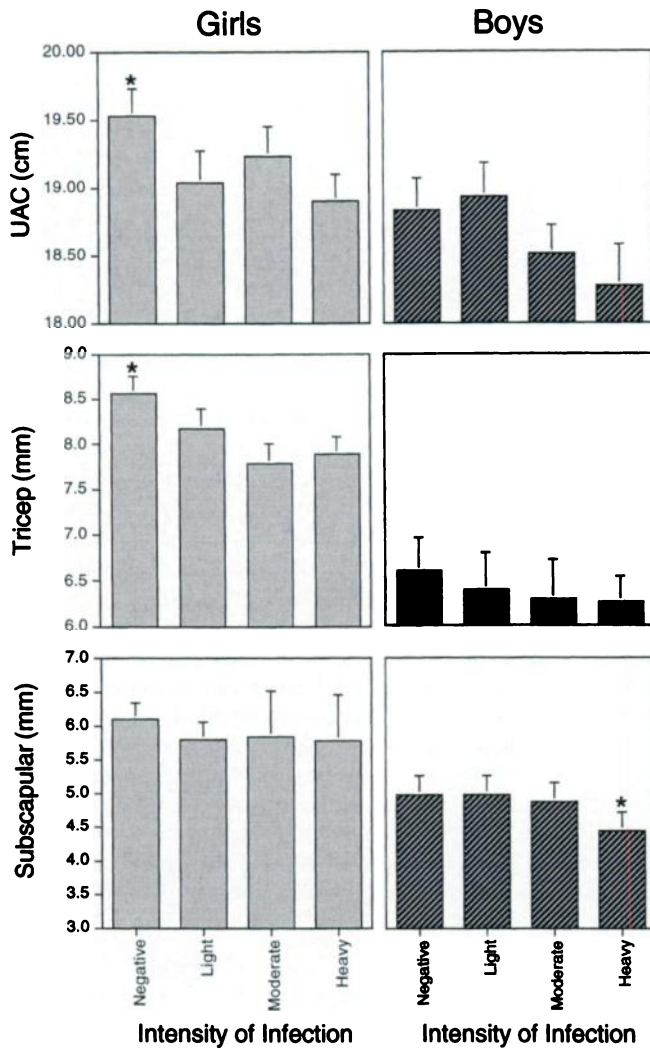


FIGURE 3. Body composition (mean \pm SEM) compared by gender and *Schistosoma mansoni* infection status using analysis of covariance. * indicates a mean measurement that is significantly different from those at all other groups ($P < 0.05$). UAC = upper arm circumference.

tion status. The mean height-for-age z-score for girls was -1.06 compared with -1.22 for boys ($P = 0.02$). The mean weight-for-age z-score for girls was -0.95 compared with -1.18 for boys ($P < 0.001$). The only difference in anthropometrics among the intensities of infection in boys was the SSF (Figures 2 and 3). This was significantly less for those heavily infected compared with those at all other intensities of infection or boys in the control group ($P < 0.05$).

Geohelminth infection and nutritional status. There were no significant differences between the groups for infection with the geohelminth *Ascaris*. *Trichuris* infection, however, was significantly associated with schistosome infection regardless of gender (Table 4). To assess whether *Trichuris* infections independently contributed to malnutrition, a two-way analysis of variance was used in a model in which z-scores were dependent variables and infection status (*Trichuris* alone, *Trichuris* plus *S. mansoni*, or *S. mansoni* alone) were independent variables. With this model, differences in both height and weight were associated with *S.*

TABLE 4
Polyparasitism in school children in Nazare, Brazil

Geohelminth infection	<i>Schistosoma mansoni</i> -infected %* (n)		Egg-negative % (n)	
	Girls	Boys	Girls	Boys
<i>Ascaris</i>	69.6 (195)	67.2 (174)	64.5 (176)	68.5 (161)
<i>Trichuris</i>	67.1 (188)	71.4 (185)	58.7 (159)†	59.1 (139)‡
Either	78.6 (220)	83.0 (215)	74.0 (202)	79.1 (186)

* Percent of all *S. mansoni*-infected or egg-negative boys or girls.
 † Significantly fewer egg-negative girls infected with *Trichuris* compared with the *S. mansoni*-infected group using the chi-square test ($P < 0.03$, $\chi^2 = 4.9$).
 ‡ Significantly fewer egg-negative boys infected with *Trichuris* compared with the *S. mansoni*-infected group using the chi-square test ($P = 0.01$, $\chi^2 = 8.2$).

mansoni infection ($P = 0.004$ and $P = 0.006$, respectively), and *Trichuris* infection did not have an additive effect.

DISCUSSION

Growth and nutritional status represent the most sensitive indicators of health in children. It is clear that infections in infancy contribute to malnutrition and poor growth up to the age of five years. After that time, the impact of bacterial and viral infections on growth is significantly less. Rather than demonstrating catch-up growth, however, the developmental profile of school-aged children in developing countries often continues to decrease relative to healthy, well-nourished populations. This is often manifest as chronic malnutrition in which height and weight are proportionately reduced, producing a normal weight-for-height index despite a failure to approach growth potential. In Nazare, the nutritional status of children continues to decline with age relative to the reference population, while the prevalence of schistosome and other parasitic infections increases. When growth and nutritional status were used as indicators, any level of schistosomiasis appears to accentuate growth deficits when superimposed on a mild community-wide level of chronic malnutrition. In contrast, the dramatic end of the spectrum of disease caused by *S. mansoni* infection consists of severe overt pathology characterized by portal hypertension, esophageal varices, colonic polyposis, nephropathy, pulmonary hypertension, or transverse myelitis. Mild deficits in growth and nutrition seem inconsequential in comparison, except that 90% of the estimated 200 million people infected are at risk for this lower level of morbidity. Infection thus contributes substantially to what is often referred to as the burden of disease. The 90% of individuals with mild or moderate intensities of infection may actually represent the major impact of schistosomiasis on a population.

In many populations, malnutrition is not evenly distributed between the sexes. This was the case in Nazare. An effect of schistosomiasis on nutritional status was apparent primarily for girls, though girls possessed a superior level of nutrition relative to boys. Many studies and surveys indicate that though the growth potential of boys is ultimately greater than that of girls, growth in boys is at the same time more sensitive to environmental insults, such as malnutrition, infection, and disease¹⁵⁻¹⁸. Boys, moreover, have been observed to respond most rapidly when an environmental stress is removed, for example, upon refeeding or treatment of disease.^{16, 18-20} In developed countries, the pattern of growth in the sexes is that boys are slightly larger from birth up to

10–12 years of age. Between 10 and 12 years, the average anthropometric measures in girls are greater, since the growth spurt on average begins two years earlier in girls than in boys. Boys later experience accelerated growth, and sexual dimorphism becomes marked thereafter. In developing countries, on the other hand, young, school-aged girls are sometimes larger than boys even before the growth spurt in girls, and the degree of adult sexual dimorphism may ultimately be reduced.²¹ Boys in the community studied here may already have such poor nutritional status that any contribution from schistosome infection does not further compromise them. Support for this hypothesis comes from a variety of observations on growth in boys assessed by size, skeletal maturation, and dental eruption.^{15–17}

Investigations in Nazare reinforce the concept of a synergism between infection and malnutrition. Neither differences in sociodemographic status nor other parasitic infections were independently related to differences in nutritional status. These factors were both related to schistosomiasis, however, and in conjunction with schistosomiasis, they were associated with worsened nutritional status. *Trichuris* infections are nearly universal and thus, difficult to discount as cofactors in malnutrition. Widespread infection with multiple parasites may contribute to the background of chronic malnutrition observed in the community. Due to the boys' greater sensitivity, multiple parasitic infections may be a major contributor to their more severe malnutrition.¹

How schistosome and geohelminth infections might be synergistic is not clear, but both are associated with mild inflammation of the bowel. Geohelminths are transmitted by the fecal-oral route, particularly by the ingestion of feces-contaminated soil. They then become resident in the intestine and are thought to cause local inflammation and mild malabsorption.^{22,23} In contrast, schistosomiasis is acquired by the active penetration of the parasite through the skin when a person enters contaminated water. The parasites eventually migrate to the veins around the intestine, but are not found in the lumen of the gut. Their eggs, however, must pass through the wall of the intestine to enter the lumen, and this provokes marked local inflammatory responses.²⁴

Methodologic constraints in this study tend to diminish the potential differences observed between the egg-negative and infected groups. The presence of eggs in stool is the most commonly used technique for the diagnosis of schistosomiasis. Because of logistic and economic limitations, one stool examination was used to designate children as egg-negative. Since egg excretion is variable from day to day and hour to hour, a single examination will sometimes miss very light infections. In a recent study of more than 200 Brazilian military recruits, one and two stool examinations were accurate 75% and 90% of the time, respectively, compared with examination of three stools.²⁵ Moderately or heavily infected individuals were rarely negative on the first examination. Up to 25% of the egg-negative children in this study may have had light infections. The effect of this error would be to diminish the statistical significance of differences between the two groups, so that our findings represent a minimum difference. The reason differences were observed, however, is that most undetected infection in the egg-negative children would be very light, and morbidity in this study as well as others is directly correlated with egg

intensity.^{26,27} Other factors may also have diminished the differences we observed. The population studied here only included those children who were attending school and complied with the request for a stool sample. Children from households with higher sociodemographic status may be overrepresented. Despite these biases against observing a difference, *S. mansoni* infection in conjunction with other parasites was significantly associated with malnutrition in school-aged children in Brazil.

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