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CHILD GROWTH AND SCHISTOSOMIASIS JAPONICA IN NORTHEASTERN LEYTE, THE PHILIPPINES: CROSS-SECTIONAL RESULTS

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Abstract. The association between schistosomiasis japonica and child growth was studied cross-sectionally in 1, 561 males and females aged 4–19.9 years residing in an endemic region of northeastern Leyte, The Philippines. Stature, weight, upper arm muscle area, and sum of triceps and subscapular skinfold thicknesses were measured and related to presence of *Schistosoma japonicum* eggs in Kato stool smears and to the intensity of infection assessed by quantitative egg count. The presence of hookworm, ascaris, and trichuris eggs was also measured. Multivariable models were used to control for the effects of age, age^2, and polyparasitism on growth. The prevalence of schistosomiasis was 31% in males and 22% in females, with the maximum prevalence in adolescence. In 8–19-year-old subjects, the intensity of schistosomiasis japonica was significantly related in males to reduced arm muscle area and sum of skinfolds (both $P < 0.01$) and in females to reduced stature, weight, arm muscle area, and sum of skinfolds (all $P < 0.01$). The greatest age-specific differences were during adolescence in both males and females. The growth retarding effects of intensity of schistosomiasis japonica were independent of the influence of other parasites, notably hookworm. Due to the magnitude of the schistosomiasis-associated growth differences in adolescence, adult body size, function and productivity may be affected.

The maximum prevalence of schistosomiasis japonica occurs in children due to high transmission from frequent water contact, but may also be due to the slow acquisition of resistance.[1–4] Previous studies of morbidity due to *Schistosoma japonicum* infection focused on hepatosplenomegaly and functional complaints. Hepatic enlargement occurs in 15–25% of all infected individuals and is more common in adolescence, with up to a 60% prevalence in 10–15-year-old individuals.[1–4] Because both maximum infection and hepatic enlargement prevalences occur during the ages of rapid physical growth and development, we began our initial community-based studies to determine the relationship between child growth and infection with *S. japonicum*. Malnutrition and physical growth have been studied in both *S. haematobium* and *S. mansoni* infections.[5–12] The overall purpose of these childhood growth and schistosomiasis japonica studies is to more fully characterize morbidity in the most vulnerable age group, and to determine if schistosomiasis exerts an influence on reduced growth for age. We report herein on cross-sectional results from a population in Leyte, The Philippines that is endemic for schistosomiasis japonica.[1, 2] The design of this study was to determine growth and nutritional differences by current infection status and by intensity of infection.

SUBJECTS AND METHODS

The study population resides in six villages from several municipalities in the rural region near Palo, Leyte, The Philippines. Three of the six villages were described in previous studies.[1, 2] These three villages have had annual surveys and treatment of infected individuals since 1981, although the prevalence of *S. japonicum* infection reached village-specific plateaus after the first three years. Three additional villages were added to the project in the 1988–1989 field season. All six villages were chosen because of the high schistosomiasis transmission rate associated with highly infective water sources, exposures via rice

farming, and the general lack of sanitation concomitant with rural poverty. The anthropometric data were first collected during the 1988–1989 field season.

A sample of 823 males and 738 females (age range 4–19.9 years) residing in these six villages had complete anthropometric and parasitologic data recorded. This sample represents 87.4% of residents of this age range based on the annual village enumerations.

One stool sample per child was collected and prepared using the Kato thick smear technique for parasitologic examination with duplicate slides and confirmation by two observers.[13] Quantitative egg counts were determined for *S. japonicum*. A 10% random sample of all slides was later examined by one of us (P. P.) in the field to check the accuracy of measurements. The error rate was < 10%. The intensity of schistosomiasis was categorized as light (1–100 eggs/gram of feces [epg]), moderate (101–400 epg), and heavy (> 400 epg). The presence or absence of eggs was also determined for ascaris (*Ascaris lumbricoides*), hookworm, and trichuris (*Trichuris trichiura*) for the total sample.

Anthropometric measurements were performed following standard techniques by examiners blinded to infection status.[14] We report herein on a subset of these measures: stature, weight, upper arm muscle area, and the sum of triceps and subscapular skinfold thicknesses. These four measures provide key summary information on bone, muscle, and adipose tissue growth, and allow some inferences about chronic and acute malnutrition. Upper arm muscle area is calculated from the upper arm circumference and triceps skinfold according to a standard formula.[14] All measures except weight were taken twice and averaged. A substudy of interobserver error in anthropometric measurements showed very high correlations (range 0.85–0.92), with the skinfold correlations lowest.

Stature and weight by age and sex were compared with the 1982 Philippine National Survey means[15] and a recently published compilation of the United States National Health and Examination Survey (NHANES) I and II growth standards.[16]

Descriptive, sex-specific analyses were performed to demonstrate growth in infected and uninfected children over the whole age range. The primary analyses were multivariable models that regressed anthropometric characters on age and age^2, intensity of schistosomiasis infection, and the presence/absence of the other parasites. The two latter factors were treated as categorical variables in the regressions. Because of the small number of heavily infected individuals, the intensity of schistosomiasis infection was categorized as not infected, light, and moderate/heavy in the multivariable models. The multivariable analyses were restricted to 8–19.9-year-old children because of the marked increase in schistosomiasis and hookworm prevalence at age eight and the initial descriptive results showing growth differences in this age range. The regression results were presented by showing 1) the probability or P values for the regression coefficients of the two parasite categorical variables and 2) the adjusted means for anthropometric measures by category of schistosomiasis infection intensity. Age-specific analyses were performed to detect anthropometric differences between infected and uninfected children at two-year age intervals. Significant differences for each two-year age interval were determined by t-tests, with tests for equality of variances. All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Inc., Cary, NC).[17]

RESULTS

Prevalence of schistosomiasis japonica increased with age to a maximum at 12–16 years in both males and females and decreased slightly thereafter (Table 1). The overall prevalence was 31.3% in males and 21.8% in females. Both males and females were also characterized by noteworthy polyparasitism (Table 1). Infection with ascaris and trichuris was ubiquitous and hookworm prevalence was 38% in males, with a maximum of nearly 50% from the age of 12–19.9 years, and 22% in females. There was a significant association between schistosomiasis and hookworm infection ($\chi^2 = 43.8$, $P < 0.0001$; n = 1, 561). Approximately 44% of children with schistosomiasis had hookworm infections, whereas only 26% of those uninfected had hookworm infections.

The distribution of intensity of schistosomiasis infection indicates that the majority had light infections (Table 2). Of the 258 infected males, 78% had light-intensity infections, 17% had moderate-intensity infections, and 5% had heavy-intensity infections. Among the 161 infected females, the intensities of infection were 77%, 19%,

TABLE 1

Parasite prevalences (%) by sex and age in northeastern Leyte, The Philippines, 1988–1989

Age (years)	n	*Schistosoma japonicum*	*Trichuris trichiura*	*Ascaris lumbricoides*	Hookworm
Males					
4–7.9	252	16.3	84.9	84.5	24.2
8–11.9	258	34.9	80.2	79.5	38.4
12–15.9	201	42.8	84.5	81.1	48.8
16–19.9	112	36.6	78.6	72.3	49.1
Total	823	31.3	82.5	80.4	38.0
Females					
4–7.9	249	16.5	87.1	86.7	18.5
8–11.9	219	24.2	80.8	84.5	24.7
12–15.9	170	25.9	83.5	77.6	19.4
16–19.9	100	23.0	84.0	78.0	30.0
Total	738	21.8	84.0	82.8	22.1

TABLE 2

Schistosomiasis japonica intensity (%) by sex and age in northeastern Leyte, The Philippines, 1988–1989

Age (years)	n	Eggs/gram of feces			
		Negative	1–100	101–400	≥401
Males					
4–7.9	252	83.7	13.9	2.0	0.4
8–11.9	258	65.1	27.9	5.8	1.2
12–15.9	201	57.2	31.3	9.0	2.5
16–19.9	112	63.4	29.5	5.3	1.8
Total	823	68.7	24.7	5.4	1.3
Females					
4–7.9	249	83.5	13.3	2.8	0.4
8–11.9	219	75.8	19.1	3.2	1.8
12–15.9	170	74.1	20.0	5.3	0.6
16–19.9	100	77.0	16.0	6.0	1.0
Total	738	78.2	16.8	4.0	1.0

and 4% for light, moderate, and heavy, respectively.

Male and female mean stature and weight in the study sample were consistently less than the national Philippine survey means and generally less than the fifth percentile of the NHANES standards. Arm muscle area in all males and females < 16 years old was consistently below the 10th percentile of the NHANES standards. Among the older females arm muscle area means approached the NHANES 25th percentile.

Subcutaneous adipose tissue growth in the study sample was closer to the NHANES standards. The sum of triceps and subscapular skinfolds in males varied between the 25th and 50th percentile, and the sum in females was consistently close to the NHANES 50th percentile.

Reduced stature in infected individuals was consistent by 10–12 years of age in both sexes, and the greatest reduction appeared at ages 16–19.9 years (Figure 1). Similar differences in weight between infected and uninfected children were apparent among males 15 years or older and females eight years or older (Figure 2). Decreased upper arm muscle area was consistently less among infected males and females (Figure 3). Above the age of eight, infected males had a smaller sum of triceps and subscapular skinfolds than their uninfected counterparts and the same difference appeared in females by age 12 (Figure 4).

Age-specific contrasts between schistosomiasis-infected and uninfected individuals revealed that the greatest growth differences were in 16–17.9-year-old adolescent males and 12–13.9-year-old adolescent females (Figures 1–4 and Table 3).

Schistosomiasis infection intensity was independently and significantly associated with reduced growth and nutritional reserves from the ages of eight to 19.9 years, when the effects of other helminths were controlled (Tables 4 and 5). Ascaris and trichuris infections were not related to any anthropometric measures in models with measurable schistosomiasis intensity. However, hookworm infection, measured as present or absent, was related to several growth indicators, and thus the final models included both hookworm infection, the intensity of schistosomiasis infection, and age and age^2 among those 8–19.9 years old.

In males 8–19.9 years of age, intensity of schistosomiasis infection was significantly associated with reduced arm muscle area and sum of skinfolds (Table 4). The adjusted means indicated an apparent direct effect of schistosomiasis infection intensity on reduced muscle and fat growth. Hookworm infection in males was not related to any of the anthropometric measures after adjustment for schistosomiasis infection intensity.

Intensity of schistosomiasis japonica was strongly and significantly related with reduced stature, weight, arm muscle area, and sum of skinfolds in 8–19.9-year-old females while adjusting for effects of hookworm infection (Table 5). There was a consistent reduction in stature, weight and arm muscle area from uninfected to lightly infected to moderately or heavily infected

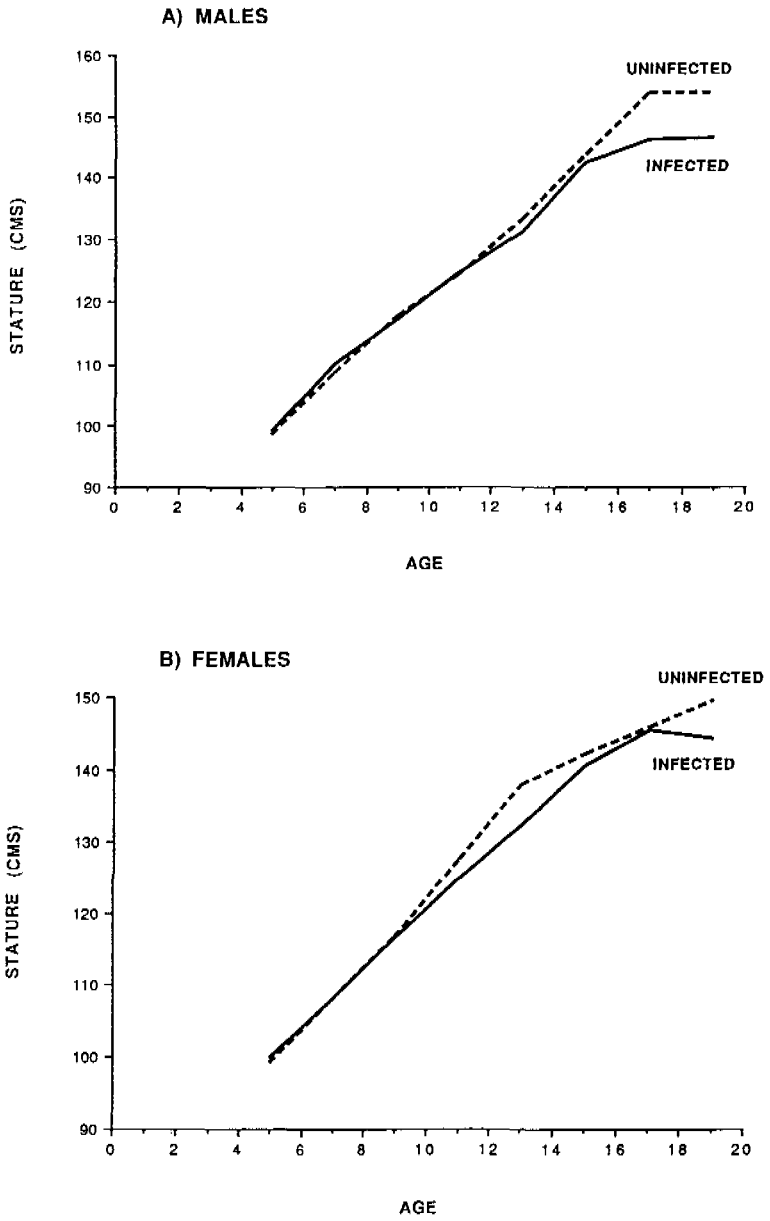

FIGURE 1. Stature by age in *Schistosoma japonicum*–infected and uninfected males (**A**) and females (**B**). CMS = centimeters.

females. Hookworm infection was significantly and inversely associated with sum of skinfolds in females.

Among males 16–17.9 years of age and females 12–13.9 years of age, schistosomiasis was significantly associated with reduced growth independent of the nonsignificant hookworm infection effects. The hookworm-adjusted anthropometric differences between schistosomiasis-infected and uninfected individuals in these sex-age groups were virtually identical to the unadjusted means in Table 3.

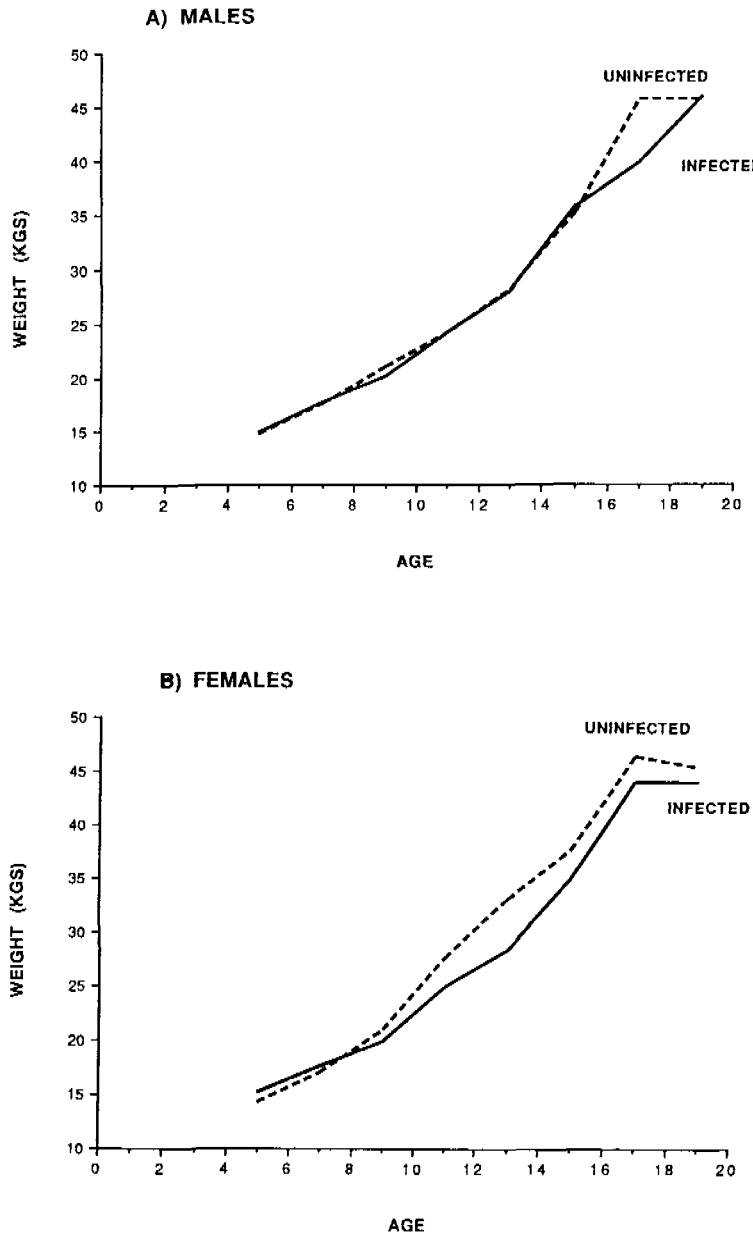

FIGURE 2. Weight by age in *Schistosoma japonicum*–infected and uninfected males (**A**) and females (**B**). KGS = kilograms.

DISCUSSION

These cross-sectional results from Leyte, The Philippines show significant and powerful disruptive influences of schistosoma japonicum infection on nutritional reserves and growth from middle childhood through adolescence. The influence of intensity of schistosomiasis japonica was independent of other helminth infections, notably hookworm. Furthermore, it appears that schistosomiasis exerted a stronger growth retarding influence cross-sectionally than hookworm infection.

These results are consistent with previous

TABLE 3

Differences in stature, weight, upper arm muscle area, and sum of skinfolds by Schistosomiasis japonicum infection status in 16–17.9-year-old males (n = 65) and 12–13.9-year-old females (n = 96) in northeastern Leyte, The Philippines

	Stature (cm)	Weight (kg)	Arm muscle area (cm^2)	Skinfolds sum (mm)
Males				
Infected (n = 25)	146.2	39.9	29.3	13.3
Uninfected (n = 40)	154.0	45.7	35.1	16.1
Difference	7.8	5.8	5.8	2.8
*P**	<0.01	<0.003	<0.01	<0.003
Females				
Infected (n = 26)	132.3	28.3	20.5	17.5
Uninfected (n = 70)	138.0	33.1	22.1	23.1
Difference	5.7	4.8	1.6	5.6
*P**	<0.02	<0.001	<0.1	<0.0001

* By *t*-test.

studies of *S. mansoni* and *S. hematobium*. In a cross-sectional study of 493 Brazilian children ages 4–14 years, the intensity of *S. mansoni* infection and splenomegaly were associated with low height, weight, and arm muscle area after adjustment for a variety of socioeconomic and water use measures.[18] In a recent review, Stephenson cites a Tanzanian study showing reduced height and weight in *S. mansoni*–infected school children relative to uninfected peers.[12] Some studies found no cross-sectional association between *S. mansoni* infection and child growth, such as a study of 138 children 7–16 years of age from St. Lucia.[7] Small sample sizes and low prevalence and intensity of infection may have made such effects difficult to detect in this and other studies.[7, 9]

In a study of 786 Egyptian children ages six months to 10 years, those with heavy *S. haematobium* infections had significantly thinner skinfolds, as a percent of WHO standards, than uninfected or more lightly infected children. However, there was no control for potential confounding by other parasitic infections that were associated with *S. haematobium* infection.[6] Stephenson also discusses several other studies of *S. haematobium* that must be considered inconclusive due to small sample sizes, lack of control for age, and intensity of infection.[12]

In a randomized treatment study of 399 Kenyan schoolchildren ages 6–16 years infected with *S. haematobium*, Stephenson and others showed that metrifonate-treated children had significantly greater six-month gains in weight for age,

TABLE 4

Regression of stature, weight, upper arm muscle area, and sum of skinfolds on age, age², Schistosomiasis japonicum intensity of infection, and hookworm infection in 8–19-year-old males (n = 571) in northeastern Leyte, The Philippines

	Stature (cm)	Weight (kg)	Arm muscle area (cm^2)	Skinfold sum (mm)
Infection*				
Negative	133.1	30.1	23.0	14.8
Light	131.7	29.2	22.0	14.2
Moderate/heavy	130.7	29.3	20.6	13.3
P values†				
Hookworm (+/−)	0.93	0.11	0.64	0.11
S. japonicum	0.08	0.30	0.01‡	0.01‡

* *S. japonicum* intensity of infection. Means were adjusted for age, age², and hookworm.

† Probability of regression coefficients in a multivariable model estimated in the regression of anthropometric measures on age, age², presence/absence (+/−) of hookworm, and intensity of *S. japonicum* infection.

‡ Significant at $P < 0.05$.

TABLE 5

Regression of stature, weight, upper arm muscle area, and sum of skinfolds on age, age², Schistosomiasis japonicum intensity of infection, and hookworm infection in 8–19-year-old females (n = 489) in northeastern Leyte, The Philippines

	Stature (cm)	Weight (kg)	Arm muscle area (cm^2)	Skinfold sum (mm)
Infection*				
Negative	133.3	32.0	21.6	23.1
Light	131.0	29.9	20.1	20.0
Moderate/heavy	128.0	27.6	18.9	21.3
P values†				
Hookworm (+/−)	0.92	0.49	0.30	0.04‡
S. japonicum	0.009‡	0.0005‡	0.0009‡	0.009‡

* *S. japonicum* intensity of infection. Means were adjusted for age, age², and hookworm.
† Probability values of regression coefficients in a multivariable model estimated in the regression of anthropometric measures on age, age², presence/absence (+/−) of hookworm, and intensity of *S. japonicum* infection.
‡ Significant at $P < 0.05$.

arm circumference for age, and skinfold thickness than the placebo group.[10] Their study design controlled for differences in other parasitic infections, especially malaria, and initial nutritional status and rendered clear evidence that *S. haematobium* infection retarded growth. It would be interesting to extend this study throughout adolescence. A further randomized treatment study of 312 children 6–17 years of age found that praziquantel and metrifonate both produced growth improvements over eight months compared with placebo, and that the reduction of *S. haematobium* infection intensity due to praziquantel was the most powerful influence on growth response to treatment.[11]

Differences among schistosomes may make cross-species comparisons difficult, as do ecologic differences among the host human populations. However, there are study design differences that are relevant to the interpretation of the present results. The present study differs from most of the previous work because of the large and representative sample of 4–20-year-old children from throughout the period of child and adolescent growth, the focus on adipose tissue and muscle, and the adjustments for age effects and polyparasitism. It is noteworthy that our results suggest profound effects during adolescence indicating potential life-long deficits in body size. Further studies of other schistosomal species should also include adolescence to determine if the same effects can be found at this time of rapid growth and development.

Study limitations included the cross-sectional design and potential influence of socioeconomic factors. Since we hypothesize that schistosomiasis and other parasites are proximate causes of malnutrition, we restricted these analyses to those variables. A full causal model including social, economic, and behavioral factors would reflect ultimate and proximate causes, and is beyond the scope of this report. We also did not want to overcontrol the relationship between schistosomiasis and growth by including socioeconomic factors that may mask the hypothesized cross-sectional relationship and its implications for treating infections in children. An additional limitation is the use of one stool collection per child, which may misclassify light infections as negative. However, this potential bias would reduce the chance to detect anthropometric differences by lowering the values of the uninfected children. Thus, the present results may be an even more conservative estimate of the hypothesized effects of schistosomiasis.

The study sample must be considered chronically malnourished since comparisons of their growth patterns with the Philippine National Survey[15] and the NHANES[16] surveys show relative growth retardation in stature, weight, and arm muscle area. However, the relatively normal sum of skinfolds suggests reasonably good very recent health and nutrition. Stephenson suggested that effects of schistosomiasis on growth may be accentuated in the presence of malnutrition due to other causes.[12] Thus, the background malnutrition in the study population may have permitted us to detect significant cross-sectional effects of current schistosomiasis infection on growth patterns. Despite the frequent reinfection of children and the presumed growth-retarding effects, the current intensity of infection status

tainly later in these children than in those from industrial nations and similar to those from other developing nations with retarded growth and delayed adolescence.[19] The ages of maximum growth difference between infected and uninfected children may coincide with early adolescence, the period of rapid growth potential. Any environmental insult on children during this period, such as helminth infection, may reduce the maximal potential bone, muscle, and fat tissue response to the hormonal influences determining adolescent growth. Growth reduction during early adolescence may have important implications for later adolescent and final adult body size, functional performance, and economic productivity. However, these are speculations that await the necessary longitudinal studies during adolescence.

There is a clear and consistent association between the intensity of schistosomiasis and delayed growth in both males and females. Uninfected individuals have the highest values for the four growth measures, those lightly infected have intermediate values, and the moderately and heavily infected individuals have the lowest values. This dose-response relationship to the level of infection suggests a biologically plausible etiology for the nutritional depletion and growth reduction associated with schistosomiasis.

Female growth appears to be affected more by schistosomiasis than male growth. From 8–19.9 years of age, the associations are stronger and the absolute differences between infected and uninfected females are larger than similar parameters in males. There is no clear explanation for this apparent sex difference in the degree of impact of schistosomiasis. This result is different from that of many growth studies in malnourished populations, which find females more buffered and less adversely affected by environmental influences.[20] Perhaps the intrafamilial and intracommunity distribution of resources to growing females is less than that to males, as has been observed in other populations.[21] Thus, specific research is needed to measure childhood sex differences in dietary intake and health care use.

The etiology of the apparent malnutrition and schistosomiasis japonica association is unknown, although a recent review for all schistosoma species suggests multiple pathways leading to a final reduced availability of cellular nutrients for growth.[12] These include reduced appetite in infected children, increased blood loss and anemia, reduced nutrient absorption, and increased nutrient loss. The anorexia of infected children has been demonstrated by a recent randomized study showing increased appetite and food intake in those treated for *S. haematobium*.[22]

Given the consistency of the demonstrated associations in both sexes at the specific ages and the relationships to the level of infection, we conclude that schistosomiasis japonica is clearly related to reduced nutritional reserves and delayed child growth, and thus contributes to morbidity in these children and adolescents. Social and economic factors may be involved in this relationship, and future analyses will focus on their role using a different subsample with detailed socioeconomic interview data. Further study of the response of infected children after treatment and construction of a representative longitudinal cohort is also needed. Analyses of the influence of malnutrition, assessed by delayed growth, on risk of reinfection are also planned.

This work highlights the key importance of studies of the more subtle but potentially more prevalent morbidities associated with parasitic infections, in addition to more specific organ pathologies. If growth decrements are not prevented or reversed, the lost growth potential in adolescence may seriously affect adult health and productivity. If these cross-sectional results are confirmed with longitudinal studies, it would seem imperative to consider annual school-based programs of schistosomiasis screening and treatment, or perhaps mass treatment of children and adolescents with praziquantel.[23]

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