Higher Serum Concentrations of DHEAS Predict Improved Nutritional Status in Helminth-Infected Children, Adolescents, and Young Adults in Leyte, the Philippines

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Abstract

Pubertal development and associated downmodulation of proinflammatory cytokines may predict improved nutritional status, independent of chronic parasite infections, in developing countries. We enrolled 731 individuals, aged 7–30 y, from Leyte, the Philippines, where helminth infections and nutritional morbidity are highly prevalent. The following data were collected: venous blood hemoglobin and serum concentrations of ferritin, dehydroepiandrosterone sulfate (DHEAS), C-reactive protein and proinflammatory cytokines (IL-1, IL-6, TNF-α, and soluble TNF receptor II); anthropometric measurements to calculate upper arm muscle area Z-score and sum of triceps and subscapular skinfolds Z-score; stool samples to determine Schistosoma japonicum and geohelminth egg counts; and responses to questionnaires assessing socio-economic status. In cross-sectional multilevel linear and logistic regression analyses adjusted for confounders, relations were assessed between 1) DHEAS and nutritional status, 2) DHEAS and proinflammatory cytokines, and 3) nutritional status and proinflammatory cytokines. Independent of age, socio-economic status, and helminth infections, increased levels of DHEAS were associated with improved nutritional status and decreased prevalence of non-iron deficiency anemia in both males and females. DHEAS showed dose-dependent inverse associations with C-reactive protein ($P = 0.08$) and the production of IL-6 ($P < 0.0001$). These inflammatory markers, in turn, were consistently associated with undernutrition and anemia. The results suggest that the puberty-associated rise in DHEAS downmodulates proinflammatory immune responses and thereby reduces undernutrition and anemia in a population experiencing a high burden of chronic helminth infections. This novel regulatory mechanism of inflammation-related nutritional morbidity emphasizes the importance of treating prepubescent children for helminth infections. J. Nutr. 137: 433–439, 2007.

Introduction

Childhood undernutrition and anemia have considerable impact on cognitive function, physical work capacity, reproduction, and overall morbidity and mortality, during both childhood and adulthood (1). In developing countries, children suffer the highest prevalence of undernutrition and anemia, as well as the highest burden of parasite infections (1,2). Chronic infections are a major cause of these morbidities; they can lead to decreased food intake and impaired nutrient absorption, cause direct nutrient losses, increase metabolic requirements or catabolic losses of nutrients, and, possibly, impair transport of nutrients to target tissues (2). Some of these mechanisms are mediated by proinflammatory cytokines; in a wide variety of chronic inflammatory diseases, proinflammatory cytokines, in particular, IL-1, IL-6, and TNF-α, have been associated with anorexia, cachexia, and anemia (1,3–5).

The host proinflammatory response determines in part the extent of detrimental effects of chronic infections on nutritional status, and nutritional status, in turn, can affect the host immune response against infections, thus establishing a maladaptive cycle between immunity and nutritional morbidity (1). Pubertal development and its associated immunological changes may play a role in the disproportionate burden of undernutrition and anemia in prepubescent children compared with adults in developing countries, independent of the effects of parasite infections. Of particular interest in this respect is the adrenal steroid hormone dehydroepiandrosterone (DHEA) and its sulfate,
DHEAS, serum levels of which are low during the pubescent years, rise during pubertal development, peak between the ages of 20–30 y, and subsequently gradually decline (6). Several studies indicate that DHEA and DHEAS, here referred to as DHEA(S), have anti-inflammatory properties; downregulation of IL-6 and TNF-α by these hormones has been reported in both experimental animal and human in vitro studies (7–12). Decreased levels of DHEA(S) associated with senescence are responsible for the accompanying increase in serum proinflammatory cytokines, a pattern that defines immunosenescence (13,14). Furthermore, immunological changes during puberty are relative to the decreased susceptibility to parasitic infections of adults compared with children (15), and evidence indicates that the puberty-associated rise in DHEAS may mediate this age-associated resistance (16–18). To our knowledge, however, no studies have examined the potential beneficial effects of DHEAS on proinflammatory cytokine-mediated nutritional morbidity in adolescents.

Using data collected in an area endemic for *Schistosoma japonicum* and geohelminth infections, and with a relatively high prevalence of undernutrition and anemia, we tested the hypothesis that 1) DHEAS is associated with better nutritional status in both males and females, independent of age, socio-economic status (SES), and helminth infection intensities; 2) DHEAS is inversely associated with serum proinflammatory cytokines, independent of age, sex, and helminth-infection intensities; and 3) these proinflammatory cytokines are independently associated with nutritional morbidity. Establishment of these relations would suggest that the anti-inflammatory effects of DHEAS contribute to the decreased burden of undernutrition and anemia in young adults compared with children in a setting of continuous exposure to chronic inflammation, independent of the intensity of helminth infections.

**Methods**

**Study design and population.** This cross-sectional study was conducted in 3 *S. japonicum*-endemic rice-farming villages in Leyte, the Philippines. Malaria is not endemic in this area. Participants were enrolled during 2 periods, in October 2002 and April 2003.

The study sample consisted of 644 *S. japonicum*-infected individuals aged 7–30 y, recruited as part of a longitudinal study investigating immune correlates of resistance to reinfection with *S. japonicum* (19), and 87 *S. japonicum* uninfected subjects aged 7–18 y, recruited during the same period as controls for a separate study evaluating the effects of helminth infection on cognitive function. In total, 74.3% (*n* = 1262/1699) of individuals aged 7–30 y, residing in the 3 study villages, were screened for the presence of *S. japonicum* infection. The prevalence of infection with *S. japonicum* in this age range was 60.0%. *S. japonicum* uninfected control subjects were recruited until a target sample size of ~100 was obtained. Individuals were eligible to participate if they provided both blood and stool samples, were not pregnant or lactating, and provided parental consent (as well as child assent), or adult consent if >18 y old.

The study was approved by the institutional review boards of Brown University and the Philippines Research Institute of Tropical Medicine. All *S. japonicum*-reinfected and geohelminth-infected subjects were treated at the end of the longitudinal study, 18 mo after enrollment.

**Blood collection, processing, and analysis.** Venipuncture was performed and blood was collected into Vacutainer tubes (Becton Dickinson) containing EDTA as anticoagulant (for hemogram) or serum separator gel (for serum cytokines, C-reactive protein [CRP], and DHEAS). A complete hemogram was obtained using a hematology analyzer (Seronol-Baker Diagnostics) as described (20). Serum cytokines (IL-1β, IL-6, TNF-α, and soluble TNF-receptor I [sTNF-RI]), CRP, and DHEAS were analyzed by use of a multiplex bead-based platform (BioRad) and custom assay kits as described (21). All pipetting and sample identification was performed by a barcode-enabled, high-speed pipetting robot (Tecan).

**Nutritional status.** The following nutritional outcomes were evaluated:

- Upper arm muscle area Z-score (UMAZ); sum of skinfolds Z-score (SSFZ; based on the sum of triceps and subscapular skinfolds); and prevalence of wasting. Height and weight were measured according to standard procedures (22). BMI (kg/m²) was calculated for all participants and BMI Z-scores (BMIZ) were calculated for subjects <20 y, as described (23). Mid-upper arm circumference was measured in duplicate and skinfolds were measured in triplicate as described (23). Test-retest and inter-rater reliability for weight, height, and skinfolds were excellent, ranging from 0.73–0.99 and 0.56–0.96, respectively. UMAZ-for-age and SSFZ-for-age were calculated for all participants using a healthy reference population (24). Z-scores indicate the deviation of a person’s nutritional status from the median of a healthy US reference population of the same age and sex (25). BMI is the index of choice for the assessment of recent undernutrition in both adults and adolescents. SSFZ reflects body fat stores, and UMAZ reflects body protein stores (22,25).

**Pubertal assessment.** Tanner staging of pubertal development was performed by 2 trained physicians according to standard criteria (26). Last menstrual period was recorded for females by use of a questionnaire.

**Stool examination.** Parasite egg counts were determined by duplicate examination of 3 consecutive stool specimens obtained from each study participant. Each stool specimen was evaluated for *S. japonicum*, *Ascaris lumbricoides*, *Trichuris trichuria*, and hookworm eggs by the Kato Katz method, as described (20).

**Socio-economic status.** A summary socio-economic status (SES) score based on questionnaire data addressing parental and child educational status, occupational status, ownership of land, and assets was calculated for each participant, as described (20).

**Definitions.** Pre- and postpubertal were defined as Tanner pubic hair development stage 1 and stage 2–5, respectively. Among females, being postmenarche was defined as having reported menstruation. Wasting was defined as BMIZ < −2 in subjects <20 y and as BMI < 17 in subjects ≥20 y. Anemia was defined on the basis of age- and sex-specific hemoglobin cut-off values recommended by WHO (27): hemoglobin <115 g/L for children aged <12 y; hemoglobin <120 g/L for males aged 12–14 y and females >12 y, and hemoglobin <130 g/L for males aged >15 y. Iron deficiency anemia (IDA) was defined as presence of anemia and serum ferritin (SF) ≤30 μg/L. Non-iron deficiency anemia (NIDA) was defined as presence of anemia and SF > 30 μg/L. Recent studies evaluating the usefulness of SF for determining iron deficiency in anemic individuals from different populations have concluded that a single cut-off of SF <30 μg/L has high sensitivity and specificity for detecting IDA, even when there is concurrent inflammation (28,29).

**Statistical analyses.** Nonnormally distributed variables (all helminth egg counts, DHEAS, CRP, and all cytokines) were log transformed [ln(n+1)]. Because serum IL-6 was undetectable (<1.45 ng/L) in a substantial proportion of subjects, it was dichotomized into responses (cytokine detectable) and nonresponses (cytokine not detectable).

Analyses were done in SAS version 9.1 (SAS Institute). *P*-values < 0.05 were considered significant. For bivariate analyses, Student’s *t* test and chi-square were used for continuous and dichotomous outcomes, respectively. All multivariate analyses were adjusted for the clustering of subjects within households using multilevel models (30). Specifically, random effect models and generalized estimating equations (GEE) models
were fit for continuous and dichotomous outcomes, respectively (30). P-values and 95% CI were based on empirical and GEE standard errors. Regression coefficients are presented in the text.

Model fit of DHEAS and DHEAS-squared was evaluated to allow linear and nonlinear associations between DHEAS and the morbidity outcomes.

All analyses were adjusted for potential confounders (sex, age, SES, and S. japonicum, A. lumbricoides, T. trichuria, and hookworm egg count), as specified. Predictor variables and covariates were centered at the overall mean for all analyses. Regression estimates were interpreted as the mean change in the outcome per log-unit change from the mean of the predictor variable for an individual with a mean value for all covariates. Because of the differential effect of puberty on body composition and hemoglobin in males and females, models evaluating the relation between DHEAS and nutritional status were stratified by sex.

Results

Descriptive characteristics. Table 1 shows descriptive characteristics of the whole cohort and stratified by sex. Males were significantly older than females, but the proportion that was postadrenarche did not differ. Nutritional status was worse among males, who also had a higher prevalence of S. japonicum and hookworm infection, higher mean CRP and IL-1, and a greater prevalence of IL-6 responses. Contrary to expectation, prevalence of IDA in males was 1.4-fold that in females even though 39.7% of females were postmenarche. Prevalence of IDA in males was 1.4-fold that in females even though 39.7% of females were postmenarche. Prevalence of A. lumbricoides infection was higher among females.

Age and nutritional status. We first evaluated whether nutritional status was better among older individuals, independent of sex, SES, and intensity of helminth infections (measured as S. japonicum, A. lumbricoides, T. trichuria, and hookworm egg count). Age was positively associated with UMAZ ($\beta = 0.06, P < 0.001$) and hemoglobin ($\beta = 0.18, P < 0.0001$). In addition, age was inversely associated with the odds of anemia ($\beta = -0.11, P < 0.0001$) and wasting ($\beta = -0.06, P = 0.007$). The association between age and hemoglobin was present even among females $>12$ y of age, in whom a physiological increase in hemoglobin during puberty is not expected ($\beta = 0.06; P = 0.001$).

DHEAS and nutritional status. We assessed associations between DHEAS and nutritional markers stratified by sex, independent of age, SES, and intensity of helminth infections. Regression coefficients are presented in Table 2. Figure 1 shows sex-stratified least-square mean Z-scores for different representative values of ln-DHEAS, based on its distribution in the study sample (10th, 25th, 50th, 75th and 90th percentiles). There was a positive quadratic association between DHEAS and SSFZ in males and females, indicating that the magnitude of improvement in SSFZ increased with increasing DHEAS levels in both sexes. In males only, a positive quadratic association was seen between DHEAS and UMAZ, as well as an inverse quadratic association between DHEAS and the prevalence of wasting. Figure 2 shows the sex-stratified adjusted prevalence of all-cause anemia, NIDA, and IDA for median values and percentiles of ln-DHEAS. In both sexes, there was a quadratic association between DHEAS and hemoglobin. There was an inverse quadratic association between DHEAS and all-cause anemia in males only. In females, however, we found an inverse quadratic association between DHEAS and NIDA. DHEAS was inversely associated with both types of anemia in males. Of note, as expected, postmenarche status among females was a significant predictor of IDA, independent of age, SES, and intensity of helminth infections (odds ratio for IDA 3.4 [95% CI 1.4–8.4; $P = 0.008$]). Menarche was

Table 1: Descriptive characteristics of the whole cohort and stratified by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort, n = 731</th>
<th>Males, n = 454</th>
<th>Females, n = 277</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>15.3 (14.9–15.8)</td>
<td>16.2 (15.7–16.8)</td>
<td>13.9 (13.2–14.6)*</td>
</tr>
<tr>
<td>Postadrenarche, y (%)</td>
<td>330 (46.1)</td>
<td>213 (48.4)</td>
<td>117 (42.4)</td>
</tr>
<tr>
<td>DHEAS, mmol/L</td>
<td>879.9 (791.5–976.1)</td>
<td>917.2 (803–1047.6)</td>
<td>819.5 (691.2–971.7)</td>
</tr>
<tr>
<td>SES</td>
<td>2.2 (1.14–2.27)</td>
<td>2.14 (2.06–2.23)</td>
<td>2.31 (2.02–2.41)*</td>
</tr>
<tr>
<td>UMAZ</td>
<td>−1.06 (−1.12 to −0.99)</td>
<td>−1.33 (−1.41 to −1.26)</td>
<td>−0.60 (−0.70 to −0.51)*</td>
</tr>
<tr>
<td>SSFZ</td>
<td>−0.37 (−0.40 to −0.33)</td>
<td>−0.35 (−0.39 to −0.30)</td>
<td>−0.40 (−0.45 to −0.35)</td>
</tr>
<tr>
<td>Wasting, y (%)</td>
<td>101 (13.8)</td>
<td>76 (10.4)</td>
<td>25 (3.4)*</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>124 (122–125)</td>
<td>124 (122–126)</td>
<td>123 (121–125)</td>
</tr>
<tr>
<td>Serum ferritin, mg/L</td>
<td>33.4 (31.0–36.0)</td>
<td>35.3 (32.1–38.8)</td>
<td>30.5 (27.0–34.5)</td>
</tr>
<tr>
<td>Anemia, y (%)</td>
<td>235 (32.4)</td>
<td>164 (36.4)</td>
<td>71 (25.7)*</td>
</tr>
<tr>
<td>IDA, y (%)</td>
<td>149 (20.5)</td>
<td>109 (27.8)</td>
<td>40 (16.3)*</td>
</tr>
<tr>
<td>NIDA, y (%)</td>
<td>86 (11.8)</td>
<td>55 (15.1)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>CRP mg/L</td>
<td>5.3 (4.9–5.8)</td>
<td>6.3 (5.7–6.9)</td>
<td>4.0 (3.4–4.5)*</td>
</tr>
<tr>
<td>TNF-α mg/L</td>
<td>26.0 (23.9–28.3)</td>
<td>27.1 (24.3–30.1)</td>
<td>24.4 (21.3–28.0)</td>
</tr>
<tr>
<td>Soluble TNF receptor mg/L</td>
<td>218.6 (201.9–235.6)</td>
<td>221.6 (200.3–245.0)</td>
<td>213.8 (187.9–243.2)</td>
</tr>
<tr>
<td>IL-1 mg/L</td>
<td>1.2 (1.1–1.3)</td>
<td>1.3 (1.2–1.5)</td>
<td>1.1 (0.9–1.2)*</td>
</tr>
<tr>
<td>IL-6 response, n (%)</td>
<td>161 (22.2)</td>
<td>115 (25.5)</td>
<td>46 (16.7)*</td>
</tr>
<tr>
<td>S. japonicum infection, y</td>
<td>644 (88.1)</td>
<td>416 (81.6)</td>
<td>228 (82.9)*</td>
</tr>
<tr>
<td>A. lumbricoides infection, y</td>
<td>535 (74.4)</td>
<td>319 (71.5)</td>
<td>216 (79.1)*</td>
</tr>
<tr>
<td>T. trichuria infection, y</td>
<td>662 (82.1)</td>
<td>413 (82.6)</td>
<td>249 (81.2)</td>
</tr>
<tr>
<td>Hookworm infection, y</td>
<td>417 (58.0)</td>
<td>283 (70.3)</td>
<td>124 (45.4)*</td>
</tr>
</tbody>
</table>

1 Values are means (95% CI) or n (%) unless otherwise noted. Males and females were compared using bivariate analyses. *Different from males, P < 0.05.
2 Defined as Tanner stage of pubic hair development >1.
3 Defined as geometric means (95% CI).
4 Defined as BMIZ <−2 in subjects aged <20 y and as BMI <17 in subjects aged ≥20 y.
5 Anemia was defined according to sex- and age-specific criteria as recommended by WHO (27). IDA was defined as presence of anemia and serum ferritin ≤30 μg/L. NIDA was defined as presence of anemia and serum ferritin >30 μg/L.
TABLE 2  Associations between DHEAS and nutritional status in helminth-infected children, adolescents, and young adults stratified by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males, n = 454</th>
<th>Females, n = 277</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In DHEAS</td>
<td>In DHEAS²</td>
</tr>
<tr>
<td>UMAZ</td>
<td>0.09 (0.013)</td>
<td>0.04 (0.0004)</td>
</tr>
<tr>
<td>SSFZ</td>
<td>0.07 (0.001)</td>
<td>0.02 (0.013)</td>
</tr>
<tr>
<td>Wasting²</td>
<td>−0.30 (0.043)</td>
<td>−0.15 (0.010)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>0.55 (&lt;0.0001)</td>
<td>0.08 (0.047)</td>
</tr>
<tr>
<td>All-cause anemia³</td>
<td>0.48 (0.0005)</td>
<td>−0.11 (0.037)</td>
</tr>
<tr>
<td>NIDA²</td>
<td>−0.32 (0.023)</td>
<td>—</td>
</tr>
<tr>
<td>IDA²</td>
<td>0.86 (0.0005)</td>
<td>0.02 (0.002)</td>
</tr>
</tbody>
</table>

Regression coefficient, P-value

1 Results are based on stratified multilevel linear or logistic regression analyses, adjusted for age, SES, intensity of helminth infection, and clustering at the household level. In-DHEAS and all covariates were centered at their mean. If associations were nonlinear, results for both In-DHEAS and In-DHEAS² are presented.

2 Defined as BMI <−2 in subjects aged <20 y and as BMI <17 in subjects aged ≥20 y.

3 Anemia was defined according to sex- and age-specific criteria as recommended by WHO (27). IDA was defined as presence of anemia and serum ferritin ≤30 μg/L. NIDA was defined as presence of anemia and serum ferritin >30 μg/L.

DHEAS and cytokines. To test the hypothesis that DHEAS has anti-inflammatory properties, we assessed the relation between serum DHEAS and cytokines and CRP in the whole cohort, independent of age, sex, and intensity of helminth infections. DHEAS was inversely associated with ln-IL-1 (β = −0.08, P = 0.001) and odds of IL-6 response (β = −0.55, P < 0.0001), and tended to be inversely associated with ln-CRP (β = −0.06 [P = 0.075]). Figure 3 shows the least-square mean levels of CRP and IL-1 and adjusted prevalence of IL-6 responses for median values and percentiles of ln-DHEAS. Surprisingly, there was a positive quadratic association between DHEAS and ln-TNF-α [β (P-value) for DHEAS and DHEAS²: 0.04 (0.39) and 0.06 (0.002), respectively]. Evaluation of least-square means for TNF-α showed a parabolic association with ln-DHEAS: TNF-α was lowest for median levels of ln-DHEAS and did not differ between low and high levels of ln-DHEAS (data not shown). DHEAS was not associated with sTNF-RI (data not shown).

Serum cytokines and nutritional status. Finally, we evaluated whether inflammatory markers that showed a dose-dependent inverse relation with DHEAS (IL-1, IL-6, and CRP) were associated with nutritional status. Table 3 shows associations between inflammatory and nutritional markers for the whole cohort adjusted for sex, age, and intensity of helminth infections. ln-CRP was consistently associated with worse nutritional status. IL-6 responses were negatively associated with UMAZ and hemoglobin and positively associated with all-cause anemia and NIDA. Stratified analyses showed that the positive association between ln-CRP and IDA was significant in males (β 0.65, P = 0.0009) but not in females, suggesting that, in this population, an inflammatory component is involved in IDA in males but not in females. Surprisingly, ln-IL-1 was inversely associated with IDA but not with any other nutritional markers.

Discussion

Previous analyses of this cohort demonstrated that 1) increased levels of DHEAS predict resistance to infection and reinfection with S. japonicum, independent of host age (31) and 2) S. japonicum is associated with undernutrition and anemia of inflammation, likely through mediation by proinflammatory cytokines (20,32). Our current findings suggest a relation between pubertal development and improved nutritional status, independent of age and intensity of helminth infections. Our data further suggest that this relation may be mediated by a decrease in maladaptive proinflammatory immune responses that accompanies increased levels of DHEAS. To our knowledge, no previous studies have assessed the relation between DHEAS and proinflammatory cytokines in children and adolescents or linked the anti-inflammatory properties of DHEAS to improved nutritional status. Importantly, we controlled for the confounding effects of SES and intensity of helminth infections, both of which are important determinants of undernutrition and anemia.

The adrenal steroid DHEAS and its active metabolite, DHEA, interconvert; DHEAS is present at much higher serum concentrations, does not undergo diurnal variation, and has a longer half-life than DHEA (13). A body of evidence indicates that DHEA(S) downregulates IL-6 and TNF-α (7–12).

Proinflammatory cytokines cause undernutrition and mediate anemia of inflammation through several pathways. First, they induce anorexia, which leads to decreased food intake (4). Second, these cytokines cause cachexia through direct metabolic changes, such as increased resting energy expenditure and increased catabolism, resulting in a negative energy balance (3). Third, they mediate anemia of inflammation by inducing 1) changes in iron metabolism, 2) decreased proliferation of erythroid progenitor cells, 3) reduced erythropoietin production and sensitivity, and 4) decreased erythrocyte life span (5). Recent evidence suggests that IL-6 regulates hepcidin expression; this newly discovered peptide is thought to be a central regulator of iron metabolism, and may play an additional role in mediating anemia during chronic inflammation by reducing intestinal iron absorption (33,34).

Nonexperimental observations do not allow conclusions in the direction of causality. Although the literature supports our hypothesis (7–12), reverse causality cannot be excluded. Proinflammatory cytokines, TNF-α in particular, have been
shown to affect DHEAS metabolism (35). Both human and animal studies indicate that TNF-α inhibits DHEAS sulfatase activity, thereby blocking conversion of DHEAS into DHEA (36,37). In line with this, serum TNF-α, but not IL-6, was positively associated with the DHEAS:DHEA ratio among patients with inflammatory bowel disease (14). Conversely, in vitro stimulation of human adrenal cells with IL-6 led to an increase in DHEA (38). Stimulation of murine macrophages with IL-1 or IL-6 had no effect on DHEAS sulfatase activity (37). Given our finding that DHEAS was inversely associated with CRP and IL-6, but not with TNF-α, the lack of evidence that IL-6 can reduce serum DHEAS strengthens our interpretation of cause and effect in this study.

In adults with chronic inflammatory diseases, serum levels of DHEA(S) are generally depressed. This may reflect a physiological adaptation to maintain cortisol levels to promote survival and homeostasis (13,14). These decreased DHEAS levels may in part result directly from a proinflammatory cytokine-mediated reduction in the expression of cytochrome P450c17, one of the principal regulators of steroidogenesis (6,35). In children, DHEAS levels may also be depressed due to chronic undernutrition, which is the major cause of pubertal delay associated with chronic disease (39). In the context of our findings, both of these mechanisms associated with chronic inflammation would lead to a relatively decreased anti-inflammatory potential that results from low DHEA(S) levels, thereby perpetuating proinflammatory cytokine-mediated undernutrition.

Limitations of this study should be addressed. First, pubertal development is inherently associated with physiological changes: hemoglobin levels increase in males, but not in females (40), percentage of fat mass increases in females and decreases in males, and the reverse occurs for the percentage of lean body mass (22). The association between DHEAS and nutritional markers may thus reflect normal physiology. By using age- and sex-adjusted markers of nutritional status (anemia and Z-scores) the limitation is partly overcome. However, even with the use of these parameters there may be misclassification based on pubertal delay relative to the reference population, which is common in developing countries (41). However, we saw a positive association between DHEAS and SSFZ among males, and between DHEAS and hemoglobin among females. Because both observations are the reverse of what one would expect based on physiological changes, this suggests our findings do not simply reflect the physiologic coincidence of increasing DHEAS and improved nutritional status. Second, selection bias may affect the ability to generalize our findings. In the general population from which this study sample was derived, inflammation-mediated undernutrition and anemia are likely less prevalent; however, this would only alter the absolute magnitude of low DHEAS-associated undernutrition, without affecting the relevant mechanism.

Our findings identify a novel mechanism regulating proinflammatory cytokine-associated nutritional morbidity that may be responsible in part for the disproportionate burden of

**Figure 2** Adjusted prevalence of anemia for different serum levels of DHEAS in helminth-infected children, adolescents, and young adults, stratified by sex. Bars represent sex-stratified adjusted prevalence of all-cause anemia, non-iron deficiency anemia (NIDA), and iron deficiency anemia (IDA) for different representative values of ln-DHEAS based on its distribution in the study sample (10th, 25th, 50th, 75th, and 90th percentiles). Error bars represent 95% CI. Results are based on multilevel logistic regression analyses, adjusted for age, SES, intensity of helminth infections, and clustering at the household level. Estimates are based on linear or quadratic associations with DHEAS (Table 2).

**Figure 3** Mean concentrations of serum CRP (A), IL-1 (B), and adjusted prevalence of IL-6 responses (C) for different serum DHEAS concentrations in helminth-infected children, adolescents, and young adults. Bars represent geometric least-square means of CRP and IL-1 and adjusted prevalence of IL-6 responses for different representative values of ln-DHEAS based on its distribution in the study sample (10th, 25th, 50th, 75th, and 90th percentiles). Error bars represent 95% CI. Results are based on multilevel linear or logistic regression analyses, adjusted for sex, age, intensity of helminth infections, and clustering at the household level. Estimates are based on linear associations with DHEAS.

### TABLE 3  Associations between markers of inflammation and nutritional status in helminth-infected children, adolescents, and young adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>ln CRP</th>
<th>ln IL-1</th>
<th>IL-6 response</th>
<th>Estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMAZ</td>
<td>0.16</td>
<td>0.05</td>
<td>0.16</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>SSFZ</td>
<td>0.04</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Wasting</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
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<td>0.08</td>
<td>0.00</td>
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<tr>
<td>All-cause anemia</td>
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<tr>
<td>IDA</td>
<td>1.11</td>
<td>0.28</td>
<td>1.26</td>
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<tr>
<td>IDA</td>
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<td>0.34</td>
<td>0.16</td>
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1 Estimates represent mean change or log odds in nutritional outcome per unit increase in log-transformed CRP and IL-1, and mean difference or log odds in nutritional outcome for IL-6 responses. Results are based on multilevel linear or logistic regression analyses adjusted for sex, age, intensity of helminth infections, and clustering at the household level. Estimates are based on linear associations with DHEAS.

2 Defined as BMI <2 in subjects aged <20 y and as BMI <17 in subjects aged ≥20 y.

3 Anemia was defined according to sex- and age-specific criteria as recommended by WHO (27). IDA was defined as presence of anemia and serum ferritin ≤30 μg/L. NIDA was defined as presence of anemia and serum ferritin >30 μg/L.
parasite-associated undernutrition and anemia among children compared with adults. Taken together with our previous findings (31), our data indicate that DHEAS is involved both in controlling intensity of _S. japonicum_ infection and in decreasing proinflammatory cytokine-associated nutritional morbidity. This dual effect of pubertal development is consistent with the age-associated epidemiologic patterns of infection and morbidity observed in many schistosome endemic communities. Importantly, our findings may also apply to children with chronic inflammatory diseases in the developed world, as some of these conditions are accompanied by undernutrition (39).

In conclusion, this study supports the hypothesis that the puberty-associated rise in DHEAS promotes the downregulation of proinflammatory immune responses and thereby reduces undernutrition and anemia in a population that experiences a high burden of chronic helminth infections. These findings contribute to our understanding of the complex relations between chronic helminth infections, inflammation, and nutritional morbidity and may be relevant for other pediatric chronic inflammatory conditions. Considering the broad detrimental impact of undernutrition and anemia (1), these findings emphasize the importance of treating prepubescent children for helminth infections to reduce nutritional morbidity.

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**Literature Cited**