

**Life history, immune function, and helminths: trade-offs among immunoglobulin E, C-reactive protein, and growth in an Amazonian population**

**Running Head: Trade-offs in IgE, CRP, and growth**

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## ABSTRACT

**Objectives:** Infection with helminths is associated with shifts in host immunity, including the increased production of immunoglobulin E (IgE) and reduced inflammation. Given limited energy budgets, these changes may involve changes in energy allocation toward competing demands. Here we test for potential trade-offs between growth, IgE, and the inflammatory marker C-reactive protein (CRP).

**Methods:** Dried blood spots and anthropometrics were collected from 162 Shuar forager-horticulturalists from a village in southeastern Ecuador. Enzyme-linked immunosorbent assays (ELISAs) were used to measure IgE and CRP. Relationships among IgE, CRP, and anthropometrics were examined in three groups: children two to seven years ( $n=63$ ), children age 8 to 15 ( $n=61$ ), and adults over age sixteen ( $n=37$ ).

**Results:** Geometric mean IgE was 1,196 IU/ml while geometric mean CRP was 1.33 mg/L. In children, IgE and CRP were negatively correlated ( $r = -.21$ ,  $p = .02$ ). Controlling for fat stores and age, IgE was associated with lower stature in children ( $t = -2.04$ ,  $p = .04$ ), and adults ( $t = -3.29$ ,  $p < .01$ ). In children there was a significant interaction between age and CRP, such that in younger children CRP was associated with shorter stature, but in older children was associated with greater stature ( $t = 2.15$ ,  $p = .04$ ).

**Conclusions:** These results suggest that infection with helminths may have hidden costs associated with immunological changes, and that these costs may ultimately affect growth and other life history parameters.

Life history theory examines the age and context-dependent resource allocations that organisms make between competing demands, including growth, reproduction, and somatic maintenance (Charnov and Schaffer, 1973; Gadgil and Bossert, 1970; Hill and Hurtado, 1996; Hill and Kaplan, 1999; Lessels, 1991; Stearns, 1976). Increasingly, interest has focused on the importance of maintenance, defined broadly as repair of injury and defense against pathogens and parasites, as an important factor in determining other life history parameters (McDade, 2005; Sheldon and Verhulst, 1996). Responding to pathogens appears to be energetically costly: fever, for example, is estimated to increase metabolic rate by 13% for every degree increase in body temperature, while sepsis or systemic infection can increase metabolic costs by 50% (Lochmiller and Deerenberg, 2000). Even mild respiratory infections without fever have been found to increase resting metabolic rate (Muehlenbein et al., 2010), while data from animal models suggest that generating an antibody response is also metabolically costly (Demas et al., 1997; Eraud et al., 2005; Martin et al., 2003). In humans, periods of illness often result in outcomes such as growth delay and stunting (Bogin, 1999; McDade et al., 2008; Victora, 1992), and across species the costs associated with mounting an immune response have been found to decrease growth, survival, and reproduction (Adamo, 2001; Klein and Nelson, 1999; Muehlenbein et al., 2010; Sheldon and Verhulst, 1996; Uller et al., 2006).

Intestinal helminths such as roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*), hookworm (*Necator americanus*, *Ancylostoma duodenale*, *A. ceylanicum*, *A. braziliense*) and threadworm (*Strongyloides stercoralis*) infect approximately a billion people worldwide (Hotez et al., 2008) and may have been part of human disease ecology throughout our long evolutionary past (Hurtado et al., 2008). The direct effects of helminths on health include anemia and malnutrition (Dreyfuss et al., 2000; Ezeamama et al., 2005; Hotez et al., 2008;

Sackey et al., 2003). Helminth infections also produce consistent changes in host immunity, shifting host T-cell populations toward a  $T_H2$  biased phenotype, characterized in particular by increased production of immunoglobulin E (IgE) and associated with corresponding decreases in  $T_H1$  and pro-inflammatory responses (Cooper et al., 2000; Fallon and Mangan, 2007; Fox et al., 2000; Hewitson et al., 2009; Maizels and Yazdanbakhsh, 2003; Yazdanbakhsh et al., 2002). This shift in immune function may have subtle health effects, with the down-regulation of  $T_H1$  and inflammatory processes resulting in poorer responses to other pathogens, such as bacteria, viruses, and even vaccines (Borkow et al., 2000; Elias et al., 2008; Hotez et al., 2008; Hurtado et al., 2003; Labeaud et al., 2009; van Riet et al., 2007). Given the costs of antibody production, the upregulation of IgE may also have hidden costs due to energetic trade-offs, especially since IgE levels can remain elevated for years even in individuals free from current helminth infections (Iancovici Kidon et al., 2005; Kalyoncu and Stålenheim, 1992).

In North American and European populations, IgE levels are typically very low, consistent with low levels of macroparasite exposure (Table 1). High IgE in these populations is usually found in individuals with allergic diseases such as asthma (e.g., Bergmann et al., 1995; Holford-Strevens et al., 1984; Lindberg and Arroyave, 1986). However, IgE levels vary significantly across human populations, with some populations having average IgE levels as much as 2,000 times greater than average levels in North America and Europe (Table 1). The highest IgE levels are found among lowland indigenous groups in Ecuador (Buckley et al., 1985; Kaplan et al., 1980; Kron et al., 2000) and Venezuela (Hagel et al., 2006; Lynch et al., 1983), who have reported geometric mean IgE in excess of 10,000 IU/ml. Although genetic factors have been shown to influence IgE levels (Weidinger et al., 2008) and IgE levels show relatively high heritability when parents and offspring experience similar environments (Grant et al.,

2008), differences between populations appear to be influenced largely by environmental factors such as exposure to helminths (Cooper et al., 2008) and other macroparasites, such as malaria (Perlmann et al., 1994, 1999). This is evidenced by studies of immigrant populations, whose IgE levels drop after approximately 10 years of moving from areas with endemic helminths to those with low endemicity (Iancovici Kidon et al., 2005; Kalyoncu and Stålenheim, 1992).

South American populations, particularly those that are indigenous or rural, are also characterized by a high prevalence of stunting (Victora, 1992). Among Ecuadorian Shuar, approximately 40% are stunted (Blackwell et al., 2009), while in Ecuador as a whole, 25-30% of children under age five are reported to be stunted, with a prevalence of 58% for all indigenous groups combined (Larrea and Kawachi, 2005).

Given limited budgets of energy, time, and other resources, natural selection produces organisms that use cues in the environment to allocate life-history trade-offs preemptively, directing developmental pathways in adaptive directions (Gluckman et al., 2007; Leimar et al., 2006; West-Eberhard, 2005). This may include down-regulating certain types of expenditure to avoid overspending. Conceptualized this way, the down-regulation of  $T_H1$  responses in individuals infected with helminths may be a life-history strategy to reduce energy expenditure or to reduce competition for other nutritional or physiological resources (Long and Nanthakumar, 2004). Similarly, growth might be down-regulated in response to early cues of pathogenicity, since higher growth rates may compete for resources and increase mortality (Mangel and Stamps, 2001). Infection patterns for helminths show consistent age patterning, with higher prevalences at earlier ages in areas with overall higher transmission rates (Anderson and May, 1985; Woolhouse, 1998; Hurtado et al., 2008). Given this pattern, age of first exposure to helminths may be a reliable cue to the likelihood of future helminth exposure.

In this paper, we examine the relationships among IgE (the predominant immune response to helminths), C-reactive protein (CRP; a biomarker indicative of inflammation), and anthropometric measurements in the Shuar, an indigenous lowland group of forager-horticulturalists from Eastern Ecuador. We hypothesize that early exposure to helminths may alter energy allocations in lasting and persistent ways, shifting energy towards helminth defense and away from other demands such as growth, reproduction, and other types of immune function, such as those involved in inflammatory responses.

We use IgE levels rather than fecal egg counts for helminths for three reasons. First, while egg counts may fluctuate with current parasite load and parasite maturity, IgE levels are more likely to also reflect a history of helminth infection (Cooper et al., 2008; Maizels and Yazdanbakhsh, 2003). Second, as a marker of helminth infection, IgE levels can be measured much more easily than helminth load, requiring participants to contribute only a finger stick blood spot (Tanner and McDade, 2007). Finally, this study is interested in the trade-off between investment in immune function and growth. Among populations with endemic helminth infection, individuals with higher levels of IgE often show increased resistance to reinfection and lower parasite loads (Faulkner et al., 2002; Hagan et al., 1991; Hagel et al., 2006; McSharry et al., 1999), suggesting that the direct measurement of helminth load alone may not accurately represent investment in defense against helminths. Indeed, several studies have failed to find trade-offs between egg counts and growth (e.g., Dickson et al., 2000; Tanner et al., 2009). However, we know of no published studies examining IgE levels and growth outcomes.

The second biomarker we examine is CRP which we use as a marker of inflammatory processes that may be affected by helminths. CRP is a nonspecific acute phase reactant that rapidly increases in plasma concentration in response to inflammation, infection, and injury

(Pepys and Hirschfield, 2003). As such, CRP levels are more labile than IgE levels, rising and falling with active infections. However, baseline CRP levels have been associated with a number of medium to long term factors such as socioeconomic status and body mass (Alley et al., 2006; Gimeno et al., 2007; Nazmi and Victora, 2007). Among the Tsimane, an Amazonian population from Bolivia, CRP is elevated in children with greater exposure to pathogens (McDade et al., 2005) and is associated with poorer short-term growth in young children (McDade et al., 2008). Despite its association with poorer growth in young children, other data suggest that CRP is associated with increased body mass and adiposity in older adults (e.g., Rexrode et al., 2003, Snodgrass et al., 2007, Visser et al., 1999).

We consider IgE and CRP as they relate to height, weight, BMI, and body fat in both Shuar children and Shuar adults. The goals of the study can be conceptualized on two levels. First, an examination of the impact of helminth infections on growth has immediate utility for understanding health in indigenous and developing populations afflicted with high helminth loads. If IgE is associated with other health and growth outcomes, this may indicate a hidden burden from helminth infections. Second, this study addresses theoretical life history models that consider a broad array of trade-offs between immune function and growth, and between multiple branches of immunity (McDade, 2003, 2005). We predict trade-offs between activation of immune function and growth, but we also predict trade-offs between activation of defenses to helminths (IgE) and inflammation (CRP) due to the known anti-inflammatory effects of helminths and the predicted energetic and physiological trade-offs between these pathways. Finally, by examining IgE, CRP, and anthropometrics across ages, we investigate whether trade-off are reflected equally in differently aged cohorts.

## METHODS

### *Ethnographic Context*

Shuar are a large indigenous population numbering about 50,000 from the Amazonas region of Ecuador, and are closely related to other groups such as the Achuar and Shiwiar who belong to what has been known as the Jivaroan language group (Descola, 1996; Harner, 1984). Traditionally, Shuar lived in scattered clusters of a few households, their economy based on horticulture, hunting, and fishing. Approximately 40% of Shuar children are stunted, and Shuar are much more likely to be stunted than both the closely related Shiwiar and Achuar, and non-indigenous children living in the same area (Blackwell et al., 2009). Although we know of no studies examining helminth infections in the Shuar, recent studies report infection rates of around 50% in other comparable Ecuadorian populations, with *Ascaris* the most prevalent helminth. These include children in rainforest villages on the western side of the Andes (Sackey et al., 2003) and Napo Runa children from the Rio Napo area in northwestern Amazonas (San Sebastian and Santi, 1999, 2000).

### *Study Village*

The data for this study were collected by the authors as part of the Shuar Life History Project (<http://www.bonesandbehavior.org/shuar>) in a village of approximately 500 people, located approximately 45 minutes by truck from the town of Sucúa, Ecuador. The dirt road to the village has only been improved in the last few years, before that the village was reached only on foot. No one in the village owns a car, but since 2008, a truck comes through about once a day to offer travel to Sucúa (providing service much like a bus). Many adults travel to Sucúa once every



week or two. Since 2000, the village has had a health clinic staffed by an auxiliary or nurse that provides vaccinations and dispenses basic medications such as albendazol (for parasites), antibiotics, acetaminophen, and B-vitamin shots for other ailments. There is no malaria in the village area, and only a few village residents that were born or had lived in other areas report having had malaria. The village also has a primary school, which most children attend. There is a water line that pipes untreated water from a spring through the central part of the village, and houses along this central road have spigots. About 80% of households get their water from the water line, while the remainder obtain water from local streams or the river. About 70% of households have outhouses (almost all without water), the rest typically use the forest and other open spaces. Electricity reached the village in 2000 and about 65% of households currently have electricity, although of these about a third use it only for lighting.

All participants gave informed consent or assent, with both parental consent and child assent for subjects under fifteen. The study was approved by village leaders, the Federación Interprovincial de Centros Shuar (FICSH) and the Institutional Review Board of the University of Oregon.

### ***Anthropometry, Blood Collection, and Analysis***

Stature was recorded to the nearest 1.0 mm using a field stadiometer (Seca Corporation, Hanover, MD). Body weight was measured in light clothing (without shoes) to the nearest 0.1 kg using a Tanita BF-558 electronic scale (Tanita Corporation, Tokyo, Japan). Skinfolts (triceps, biceps, superiliac, and subscapular) were measured three times to the nearest 0.5 mm with Lange skinfold calipers without clothing (Beta Technology, Santa Cruz, CA). Blood samples were collected following standard procedures to collect dried blood spots (McDade et al., 2007). Briefly, a finger prick using a sterile, disposable lancet was used to obtain three to five 50 $\mu$ L

drops of whole capillary blood spotted onto standardized filter paper (No. 903; Whatman). Blood spot samples were dried for four hours and then sealed in airtight bags with desiccant and frozen in the village clinic freezer for 1-3 weeks. Blood spots were kept cold with freezer packs for transport to the Ecuadorian capital, Quito. They were allowed to come to room temperature for transport by plane to the University of Oregon (approximately 12 hours), after which they were stored at -30°C until analysis.

### ***Biomarker Assays***

IgE and CRP levels were determined by enzyme-linked immunosorbent assay (ELISA) in Snodgrass' laboratory at the University of Oregon. IgE was measured using a commercially available kit (Bethyl Labs, Inc.: #E80-108 and #E101) adapted for use with blood spots (Tanner et al., 2007). IgE levels were checked against controls with known concentrations (Bio-Rad; Liquichek Immunology Control; #590X). In addition, matched blood spot and serum samples from six individuals were analyzed to verify that blood spot and serum results are comparable. The values obtained from dried blood spots were highly correlated with the values from serum ( $r = 0.98$ ,  $p < .001$ ). Since dried blood spot values were close to serum values no conversion factor was applied. However, for reference the fit line between IgE and serum is as follows:  $IgE_{\text{serum}} = 0.965 \times IgE_{\text{DBS}} - 3.458$  (IU/ml).

CRP levels were determined according to a published protocol for a high-sensitivity assay (McDade et al., 2004) modified for use with different coating (Biodesign #M86005M) and detection (Biodesign #M86284M) antibodies since the antibodies from the original protocol are no longer available in the U.S. The modified protocol has been validated against both the published protocol and against blood plasma samples (T. McDade, personal communication).

CRP values were converted to serum equivalent values using the parameters from the protocol validation (T. McDade, personal communication):  $CRP_{\text{serum}} = 2.36 \times CRP_{\text{dbs}} + 0.39$ .

### *Age Estimation*

Approximate birthdates were available for most Shuar children. In general, these birthdates are accurate to the month, particularly for children born after the health clinic was established in the study village in 2000. For adults, ages were less accurate, particularly for individuals older than approximately forty. Many had birthdates on their government identification (by law all Ecuadorians are required to register for identification). These were used but were crosschecked with extensive genealogical information collected on individuals in the village. Geneologies included siblings and offspring, given in order of birth. Overlapping geneologies were collected from multiple informants in order to cross-check information.

### *Age-standardized Variables*

Commonly, z-scores based on international standards are used to evaluate growth. However, for Shuar, z-scores based on NHANES and WHO reference values show declines with age, with Shuar adolescents having lower z-scores than young children (Blackwell et al., 2009). Due to this confound with age, these z-scores were determined to be potentially inappropriate for Shuar-only comparisons across ages. Instead, age-standardized residuals (e.g., Hagen et al., 2006) were calculated for height, weight, BMI, weight-for-height (WFH), and the sum of four skinfolds (triceps, biceps, subscapular, superiliac). Height, weight, BMI, WFH, and skinfolds were fit with quadratic models. Skinfolds were fit separately by sex, since skinfolds differed

significantly between males and females. For the other measures, there were no significant differences by sex after controlling for age, so variables were not standardized for sex. Age terms were highly significant in all models. Model fits were very high for most anthropometric measures (height  $R^2 = 0.883$ , weight  $R^2=0.855$ , BMI  $R^2= 0.548$ , WFH  $R^2=0.954$ ), although somewhat lower for male skinfolds (Females  $R^2=0.663$ , Males  $R^2=0.219$ ). Standardized residuals are referred to hereafter with the suffix -SR (e.g., Height-SR). To allow for residuals to be expressed in easily interpretable units (centimeters and kilograms) we also calculated unstandardized residuals, referred to with the suffix -UR.

### *Analysis*

Analyses were done in PASW Statistics 18.0 for windows (SPSS Inc.), including data transformation, Pearson correlations, t-tests, and ANOVAs. As with many biomarkers, IgE and CRP had highly skewed distributions which were normalized by natural log-transformation so that standard parametric statistics could be used. Log-transformations and geometric means are commonly used when analyzing both IgE (see Table 1 and references therein) and CRP (e.g., Nazmi et al., 2009; Pearson et al., 2003; Rexrode et al., 2003; Willems et al., 2010). The log-transformed values are referred to as lnCRP and lnIgE. Before log transformation, CRP was converted into units of mg/ml, instead of the standard mg/L in order to avoid having negative values after the log transformation. All analyses were done on log-transformed values. T-tests were 2-tailed with equal variance assumed. Regression parameter estimates were computed using the univariate general linear model procedure. Due to colinearity between lnCRP and lnIgE models were run separately with each of these measures.

### *Control for Phenotypic Correlation*

Since the analysis of life history trade-offs may be confounded by phenotypic correlation—the fact that individuals with greater overall energy may redirect more energy into multiple pathways, leading to apparent positive, instead of negative correlations between trade-offs—skinfold thicknesses were used as proxies for energy availability and entered into regression models as control variables (McDade et al., 2008). Other studies have attempted to use measures of household wealth to control for energy availability, but have generally found little effect (e.g., Hagen et al., 2006; McDade et al., 2008). In our sample, inventories of household goods were available for 68 of 120 children. These were used to create a composite household wealth score. Including this score in regression models significantly reduced the significance of model parameters, but this appeared to be due to the reduced sample sizes as model parameters were in the same direction and of roughly equivalent magnitude. Additionally, this wealth variable was not significant or near-significant in any model, and did not correlate with any outcome variable. For this reason we do not report further on models including this wealth variable.

## **RESULTS**

### *Sample Characteristics*

Table 2 gives the sample characteristics by age group. IgE values were substantially elevated compared to U.S. NHANES values (2005-2006), but were normally distributed following log-transformation, suggesting the higher values do not represent a change in the skewed distribution of IgE, but rather a shift in the entire distribution towards higher levels (Fig. 1). The geometric mean IgE for Shuar of all ages was 1,196 IU/ml, compared to 52 IU/ml in the

NHANES sample. However, compared to other indigenous and rural populations, particularly those in neo-tropical South America, Shuar values are unexceptional (Table 1). For example, IgE levels among the Waorani, also from Eastern Ecuador, have been reported to be around 10,000 IU/ml (Buckley et al., 1985; Kaplan et al., 1980; Kron et al., 2000). Shuar values are instead closer to those found in highland areas of Ecuador (Cooper et al., 2008) and among lowland Ecuadorian Quechua (Kron et al., 2000). We can only speculate about the exact reasons for this, but we do know that the study village, which is located in the Upano Valley, has better access to health care, including treatment for helminths, than Shuar villages located further to the East. Additionally, even today Shuar are a more market integrated population than Waorani (Lu, 2007), and these Waorani studies were conducted 10-30 years ago when areas of Eastern Ecuador were significantly less developed than they are today.

Geometric mean CRP for all ages was 1.33 mg/L (arithmetic mean: 2.02 mg/L, median: 1.13 mg/L). Only 3.6% had CRP values  $\geq 10$  mg/L, a commonly used cutoff indicative of active infection, while 15% had CRP values  $\geq 3$  mg/L, a common cutoff indicative of elevated values (Pearson et al., 2003). For comparison, in the 2005-2006 NHANES data the geometric mean value CRP is 1.17 mg/L (arithmetic mean: 3.62 mg/L, median: 1.20 mg/L), while 7.6% have values  $\geq 10$  mg/L, and 26% values  $\geq 3$  mg/L. Overall the distribution of Shuar CRP values was narrower than the NHANES distribution (Fig. 1) but mean  $\ln$ CRP values did not differ significantly between Shuar and NHANES ( $t=1.05$ ,  $p=0.29$ ).

In some studies, individuals with CRP  $> 10$  mg/L are excluded from analysis in order to examine baseline CRP rather than CRP due to acute infection (e.g., Pearson et al., 2003; Snodgrass et al., 2007). Following this practice, we excluded from further analysis one 38 year old female with a CRP of 16 mg/L who was clearly an outlier and likely to be suffering from an

acute infection (the next highest adult CRP was 2.98 mg/L). We considered using similar exclusion criteria for the children under age fifteen. However, the normal distribution of CRP in the children extends much higher than in adults, and it was not clear that the five individuals with CRP > 10 mg/L were outliers (10 mg/L is approximately 2.4 standard deviations above the mean for log-transformed values). We therefore ran analyses both with and without these children. Including the children improved the significance of the findings without changing the direction or magnitude of the effects. We therefore decided to include all children in the analysis. The sample characteristics in Table 1 show the final sample after the single exclusion.

### *Children's Growth and Immune Function*

**Age patterning of IgE and CRP.** Serum IgE levels were low in the youngest study participants, but progressively higher in participants up to about age eleven, with lower levels in participants older than this (Fig. 2). In contrast, CRP was highest in the youngest individuals and then progressively lower in older participants. The decline in CRP with age was highly significant ( $F_{1,124} = 11.04$ ,  $p < .01$ ). The age profiles for CRP and IgE suggest that early in life innate immunity is the predominant response, but that in older individuals specific responses are more pronounced.

Given the age profiles of IgE and CRP, we expected them to negatively correlate and this was indeed the case ( $r = -.28$ ,  $p < .01$ ,  $df = 126$ ). However, the correlation persisted after controlling for age (partial correlation controlling for age and age<sup>2</sup>,  $r = -.21$ ,  $p = .02$ ,  $df = 122$ ), and controlling for both age and fat stores (Sum4-SR) ( $r = -.24$ ,  $p = .01$ ,  $df = 144$ ). The results

suggest the negative correlation between IgE and CRP is not merely a consequence of the age pattern, but may represent a more fundamental trade-off between different immune responses.

**Trade-offs between Immune Function and Growth.** We next examined the relationship between growth and biomarkers (Table 3). We tested for relationships with three anthropometric measures: Height-UR, Weight-UR, and BMI-UR. Skinfolds thicknesses (Sum4-SR) were used to control for energy availability in other models, but were also used as a fourth dependent variable. However, no significant relationships with Sum4-SR were found, so these results are not reported.

Without controlling for energy stores using skinfold thicknesses there were no significant associations between anthropometrics and either lnCRP or lnIgE in the children's sample as a whole. However, once the effect of skinfolds was controlled for, lnIgE had a significant negative association with Height-UR, with each 1 unit increase in lnIgE associated with a decrease of 1.2 cm in Height-UR ( $t = -2.04$ ,  $p = .04$ ). We also found that controlling for skinfolds there was a trend toward lower Weight-UR with higher lnIgE ( $\beta = -0.51$ ,  $t = -1.67$ ,  $p = .10$ ). LnIgE did not significantly predict BMI-UR and there were no overall significant associations between lnCRP and any anthropometric measure.

When interaction terms between biomarkers and skinfolds were added we found significant interactions between lnIgE and Sum4-SR on Weight-UR and BMI-UR. Since skinfold residuals are centered on zero this means that lnIgE is associated with higher weight and BMI in individuals with thicker skinfolds, but lower weight and BMI in those with low skinfolds (Weight-UR:  $\beta = .72$ ,  $t = 2.37$ ,  $p = .02$ ; BMI-UR:  $\beta = .21$ ,  $t = 2.12$ ,  $p = .04$ ). Significant interactions with lnCRP were not found (not shown).



Since IgE and CRP are closely linked to age, and since there is a transition in the balance between IgE and CRP around age seven, we hypothesized that the relationship between IgE, CRP, and growth might also vary with age. We therefore split the sample into two subsamples, age zero to seven and age eight to fifteen. We chose to divide at age eight because this is close to the approximate age at which the balance between IgE and CRP shifts, and also because this creates two subsamples of approximately the same size. We then repeated analyses to test for age group interactions.

For IgE there was a tendency toward greater negative effects in the older age group. However the interaction did not reach significance for any dependent variable. When the sample was divided by age, the relationship between lnIgE and height was only significant in 8 to 15 year-olds. In the older age group a one unit increase in lnIgE was associated with a 1.5 cm decrease in height ( $t = -1.96, p = .05$ ). Similarly, the interactions between lnIgE and Sum4-UR on Weight-UR ( $\beta=0.90, t=1.40, p=.01$ ) and BMI-UR ( $\beta=0.90, t=1.40, p=.01$ ), were significant only in the 8 to 15 year-olds and not in the zero to seven year-olds.

Although the overall main effects of CRP were not significant, analyzed by age group we found opposite trends for the association between lnCRP and Height-UR (Table 3). In younger children, CRP was associated with a decrease in Height-UR of 1.27 cm/unit lnCRP ( $t=1.56, p=.12$ , controlling for Sum4-SR), while in older children it was associated with an increase of 1.29 cm ( $t=1.68, p=.10$ ). Although separately these parameters were not significantly different from zero, analyzed together the two associations were significantly different from one another (interaction with age group:  $\beta=2.32, t=2.15, p=.03$ ). We did not find any significant relationships between lnCRP and either Weight-UR or BMI-UR (not shown).

To make these results more interpretable we divided the sample based on height and compared lnCRP and lnIgE in individuals with standardized residuals one standard residual either below or above the mean of zero (Fig. 3). For simplicity we refer to these groups as taller and shorter. For the older children, shorter individuals have a geometric mean IgE of 2,402 IU/ml, compared to only 804 IU/ml in the taller group ( $t=3.45$ ,  $p < .01$ ,  $df=21$ ). In the younger group IgE is virtually identical in the taller and shorter children (1,630 vs. 1,565 IU/ml,  $t=.08$ ,  $p=.93$ ,  $df=15$ ). As with CRP, we found a significant interaction between age group and height group in predicting IgE levels ( $F_{1,36} = 4.18$ ,  $p = .05$ ). Controlling for skinfold thickness did not significantly affect these results, nor was the relationship between skinfolds and lnIgE significant.

The association with growth is reversed for CRP. In the older children, taller individuals had a geometric mean CRP of 2.0 mg/L, compared to 0.91 mg/L for the shorter individuals ( $t=3.45$ ,  $p=.03$ ,  $df=21$ ). For younger children the direction of the relationship was reversed: shorter individuals had a geometric mean CRP of 1.6 mg/L vs. 0.87 mg/L in taller individuals ( $t=1.72$ ,  $p=.11$ ,  $df=15$ ). With the two groups entered into an ANOVA together, there is a significant interaction between age group and height status in predicting CRP levels ( $F_{1,36}=7.92$ ,  $p < .01$ ). As with IgE, Sum4-SR was not significant in these models and did not substantially alter the significance of the interaction.

### ***Adult Anthropometrics and Immune Function***

Given the relationships among IgE, CRP, and growth in Shuar children, we hypothesized that these relationships might persist into adulthood, particularly if they represent long-term allocations of energy. We therefore examined the relationship between IgE, CRP, and

anthropometrics in Shuar adults. We used the available sample of adults over age eighteen (21 females, 16 males) from the same study village. Scatterplots of IgE and CRP versus anthropometrics suggest that IgE is associated with lower values on all anthropometric measures, and CRP with greater values on all measures (Fig. 4). Despite opposite associations with anthropometrics, IgE and CRP were not significantly correlated in the adult sample, although the association remained negative (controlling for age and sex:  $r = -.26$ ,  $p = .14$ ,  $df = 32$ ; controlling for age, sex, and skinfolds:  $r = -.11$ ,  $p = .55$ ,  $df = 28$ ).

We used least squares models to estimate parameters for the relationship between IgE and CRP on anthropometric variables (Table 4). We ran models both with and without controlling for skinfolds, while all models controlled for sex and age. In the models without skinfolds we found highly significant partial correlations between IgE and adult anthropometrics. In fact, IgE accounted for 26% of the variance in height, 25% of the variance in weight, and 20% of the variance in BMI. For every one unit increase in  $\ln$ IgE, adult height was found to be lower by 2.8 cm ( $t = -3.29$ ,  $p < .01$ ), weight by 5.7 kg ( $t = -3.24$ ,  $p < .01$ ), and BMI by 1.6 kg/cm<sup>2</sup> ( $t = -2.80$ ,  $p < .01$ ). Unlike the sample of children,  $\ln$ IgE significantly predicted skinfold thickness in adults, with skinfolds decreasing by 8.7 mm per unit increase in  $\ln$ IgE ( $t = -2.30$ ,  $p = .03$ ). Controlling for skinfolds reduced the association between IgE and other measures, so that it accounted for 17% of the variance in height and weight and no longer has a significant relationship with BMI. Models were also run with interactions between IgE and skinfolds, but no significant interactions were found (not shown).

CRP positively predicted all anthropometrics, though with lower significance. CRP accounted for only 7% of the variance in height, 15% of the variance in weight, 16% of the variance in BMI, and 10% of the variance in Sum4. Each one unit increase in CRP was

associated with an increase of 2.0 cm in height ( $t = 1.56$ ,  $p=.13$ ), an increase of 6.4 kg in weight ( $t = 2.42$ ,  $p=.02$ ), an increase of 2.0 kg/cm<sup>2</sup> in BMI ( $t = 2.48$ ,  $p=.02$ ), and an increase of 9.7 mm in skinfolds ( $t = 1.86$ ,  $p = .07$ ). After controlling for Sum4 none of these remained significant, although Sum4 was highly significant in all of these models. The results suggest that much of the relationship between CRP and other measures is mediated by an association with body fat. As with IgE, we ran models with interaction terms, but found no significant interactions between IgE and Sum4 (not shown).

## DISCUSSION

In this study, we examined the relationships among IgE, CRP, and anthropometric measures in three Shuar age groups: under seven years, eight to fifteen, and over eighteen. In both children and adults, IgE and CRP were negatively correlated, consistent with our prediction that these would trade-off due to a shift in T-cell populations and corresponding changes in inflammatory cytokine production. In the children, there was also a significant age-related transition between high CRP and high IgE, with CRP declining throughout childhood and IgE increasing rapidly in the first five years of life.

The relationships among IgE, CRP, and anthropometrics varied with age. In adults, controlling for skinfolds eliminated the association between height, weight, BMI, and CRP, while improving the significance of the relationship with skinfolds. In contrast, we found IgE to be associated with poorer growth in stature and lower adult height. The relationship with IgE was much more pronounced later in childhood and in adults. In adults, IgE accounted for at least 17% of the variance in height. IgE also interacted with body fat stores in its relationship with the weight and BMI of older children, such that children with lower body fat and high IgE had lower

weights and BMIs. The results are largely consistent with our predictions. We had predicted that IgE would be associated with poorer growth due to the expected long-term costs of maintaining a humoral response to helminths. Although we did not originally predict it, the fact that the relationship increases with age supports this hypothesis, since we would expect that maintaining high IgE levels would have cumulative costs over time. Additionally, humoral responses to helminths take a significant length of time to develop (Woolhouse and Hagan, 1999), meaning that we would not expect to find high IgE levels or corresponding trade-offs in the youngest children.

From a Western perspective, the fact that IgE accounts for 17% of the variance in adult height may seem incredible, given the dramatic inter-individual variation in height in places like the US. However, it is important to note that North Americans come from a wide variety of backgrounds with different genetic dispositions, family histories, and so on. The Shuar adults in this study are from a single village composed primarily of three or four extended families. In fact, based on genealogies we collected in the village, the mean coefficient of relatedness between individuals in this study is .026 (SD +/- 0.10), approximately equivalent to the relatedness of second cousins. Thus, all of the individuals in this study not only have the same ethnic background but are also closely related to one another. It is therefore likely that they share similar genetic propensities and potentials for growth. As a consequence, we would expect a greater percentage of the variation in anthropometrics in this population to be due to environmental and developmental factors, while the heritable variance should be low.

We had also expected CRP would be associated with poorer growth, as another marker of investment into immune response. This was the case in young children, consistent with other reports (McDade et al., 2008). However, we were surprised to find a positive association

between height and CRP in older children and adults. In adults this relationship was confounded with an association between CRP, height, and fat stores. The association with fat stores in itself is not surprising since a number of studies have found associations between CRP and body mass in adults (e.g., Rexrode et al., 2003, Snodgrass et al., 2007, Visser et al., 1999), and CRP has been shown to positively correlate with lifetime weight gain, particularly among those who were stunted as children (Nazmi et al., 2009; Tzoulaki et al., 2008). However, in the older children, controlling for body fat improved the significance of the association between IgE and height, and did not significantly affect the interaction between CRP and age group. Similarly body fat did not affect the difference in CRP levels between children with low standardized residuals for height and those with high standardized residuals. In children, at least, the effect appears to be largely independent of body fat.

Before discussing a possible interpretation of these findings, we should point out several important caveats. First, since this study uses only a single measure of IgE and CRP, we cannot definitively say that these associations represent persistent changes in allocation. The negative correlation between CRP and IgE for example, may represent short term trade-offs in response to new infections, as new infections first trigger inflammatory responses and later humoral responses. However, two factors argue against this interpretation as the sole cause of the negative correlation. First, the associations among CRP, IgE, and growth argue for persistent effects in these individuals. Second, although IgE fluctuates with factors such as treatment for helminths (Cooper et al., 2008), high IgE levels are also known to persist for significant lengths of time (Kalyoncu and Stålenheim, 1992; Iancovici Kidon et al., 2005). Of greater concern is the lability of CRP levels, which fluctuate with injury and illness. While we have excluded one adult with greatly elevated CRP and excluded potential study participants that were known to be sick at the

time of blood collection, we cannot definitively say that the CRP measured in this study does not represent short-term, low level infections. However, we can argue that all else being equal, individuals with down-regulated inflammatory processes should have lower CRP, even during active infection. In effect, we expect the known lability of CRP to create additional noise around the central signal, but not to eliminate the main effect. Correlations with CRP should therefore require larger sample sizes to detect. Perhaps for this reason, in this study associations with CRP were all of lower significance than associations with IgE.

Taking these factors into consideration, we suggest the following interpretation: early pathogenic insults lead to generic inflammatory responses, as evidenced by high CRP. CRP is therefore associated with early pathogenic insults and corresponding reductions in growth. However, these early insults trigger the development of specific defenses. Since these defenses are responding to helminths, the  $T_H1/T_H2$  balance is also affected. Children who have high CRP in early childhood grow up to have lower CRP and higher IgE later in childhood, due to early shifting of this balance. With more energy shifted into specific responses (IgE), less is directed towards growth. Thus, children with high IgE later in life also have poorer growth. In contrast, high CRP is, in part, indicative of a history without sufficient pathogen exposure to shift energy into maintaining specific defenses. Thus, CRP is positively associated with growth and adult height. This is not to say that inflammation itself is not also costly, simply that individuals who have not paid the continuing costs high IgE are more prone to high CRP due to a lack of anti-inflammatory processes.

This interpretation draws on theoretical predictions about the types of solutions organisms should evolve to address resource allocation problems. These solutions should reflect not just environmental demands (e.g., defending against helminths vs. defending against viral

infections) but also what might be thought of as *immune strategies*. Organisms that frequently experience infection should invest relatively more in “standing forces” – baseline defenses that prevent infection. If these frequent pathogens are of the same or similar type to one another, the organism should maintain specific defenses to these infections, likely in the form of humoral responses (antibodies). In contrast, organisms exposed to constant but unpredictable infections may be better served by maintaining high baseline levels of generic defenses, such as those involved in inflammation. Finally, organisms that are infrequently exposed to pathogens or parasites may be better served by developing relatively few “standing forces,” instead relying on non-specific responses to a greater degree.

Since individuals in helminth endemic areas are frequently reinfected, investing in “standing forces” seems likely to be a preferred strategy for this particular class of parasite. Additionally, for helminths, age of first infection is likely to be a reliable cue indicative of the likelihood of future infection (Anderson and May, 1985; Woolhouse, 1998). Thus, there is sufficient reason to predict that organisms, including humans, may have evolved strategies to preemptively allocate energy in response to helminth infection.

We caution that this interpretation is largely speculative. It is consistent with the findings in this study, but cannot be fully supported without longitudinal data to back up the cross-sectional data presented here. Additionally, cohort effects may affect the changes in associations found across age groups. Adult Shuar may not have experienced the same pathogenic environment as more recent cohorts, due to changes in health care and lifestyle in recent years. If this is the case, then longitudinal inferences from cross-sectional data such as we present here may be suspect. However, at least one other study conducted in a longitudinal sample has found



that individuals experiencing higher levels of microbial exposure in infancy have lower levels of CRP later in life, consistent with the interpretation we suggest (McDade et al., 2010).

Whether this model is ultimately supported by future studies, the results presented here have more immediate implications for understanding health in indigenous populations, particularly in South America. The high prevalences of stunting in these populations have remained something of a mystery, since children show few signs of malnutrition and energy and protein intake in many cases appears sufficient (Godoy et al., 2005; Victora, 1992; Blackwell et al., 2009). The finding that IgE is negatively associated with growth and also adult height suggests that helminth infections may have hidden effects that have been previously overlooked, perhaps because they are not direct effects but the consequence of changes in life-history trajectories. An important caveat on this interpretation is that we cannot completely separate the costs imposed by parasite load and the costs entailed in defending against parasites. It may be that production of humoral responses is not itself costly, but that the costs come from the parasite that causes the rise in IgE. However, since IgE is associated with improved resistance to helminths, and frequently with lower pathogen loads (Faulkner et al., 2002; Hagan et al., 1991; Hagel et al., 2006; McSharry et al., 1999) we might predict exactly the opposite relationship with growth if this were the case, with poorer growth in those with poorer resistance. Additionally other studies have failed to find associations between egg counts and growth (Dickson et al., 2000; Tanner et al., 2009). Hopefully, future studies measuring both helminth load and IgE will help to settle this debate.

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Table 1. IgE levels by population as reported in the literature

Region	Population	G. Mean (IU/ml)	Reference	n	Ages
S.A.	Multiple indigenous groups, Venezuela	13,088	Lynch <i>et al.</i> , 1983	274	18.5±13.6
S.A.	Waorani, Ecuador	10,153*	Kaplan <i>et al.</i> , 1980	227	all ages
S.A.	Dicuron (Waorani), Ecuador	10,572*	Kron <i>et al.</i> , 2000	31	15-75
S.A.	Waorani, Ecuador	9,806	Buckley <i>et al.</i> , 1985	229	all ages
S.A.	Warao, Venezuela	7,004	Hagel <i>et al.</i> , 2006	159	8.6±2.5
S.A.	Dicuron (Waorani), Lago Agrio, Ecuador	4,143*	Kron <i>et al.</i> , 2000	8	adults?
Asia	Indonesia	3,162	Terhell 2002	167	0 to 10 and adults
Asia	Tibetan (living in Nepal)	2,930	Buckley <i>et al.</i> , 1985	39	all ages?
Asia	Indonesian	2,570	Wahyuni <i>et al.</i> , 2005	466	5 to 84
S.A.	“Slum” of Caracas, Venezuela	2,423	Hagel <i>et al.</i> , 1993; 1995	85	8.5±2.5
Africa	Liberia	2,123	Perlmann <i>et al.</i> , 1994	57	adults
<b>S.A.</b>	<b>Shuar, Ecuador</b>	<b>1,196</b>	<b>This study</b>	<b>163</b>	<b>2 to 67</b>
S.A.	Quichua, Ecuador	1,189*	Kron <i>et al.</i> , 2000	16	adults?
S.A.	Brazil	1,047	Grant <i>et al.</i> , 2008	822	26.9±18.7
S.A.	Pichincha, Ecuador	1,004	Cooper <i>et al.</i> , 2008	1,632	grades 2 to 7
Africa	Ethiopian Born (1-3 months in Israel)	1,016*	Iancovici Kidon <i>et al.</i> , 2005	11	13.7±1.0
Africa	Ethiopian Born (One year in Israel)	1,292*	Iancovici Kidon <i>et al.</i> , 2005	11	14.7±1.0
Africa	Nigeria	973	McSharry <i>et al.</i> , 1999	92	5 to 15
Africa	Gambia (Rural school children)	962	Godfrey, 1975	131	schoolchildren
Asia	Thailand	647	Perlmann <i>et al.</i> , 1994	23	adults
S.A.	School children, Venezuela	450	Hagel <i>et al.</i> , 2006	70	7.6±2.5
Africa	Tanzania	397*	Perlmann <i>et al.</i> , 1999	230	0 to 29
Africa	Gambia (Urban school children)	368	Godfrey, 1975	60	schoolchildren
Africa	Gambia (Rural)	364	Nyan <i>et al.</i> , 2001	142?	> 15
Africa	Gambia (Urban)	332	Nyan <i>et al.</i> , 2001	142?	> 15
Africa	Madagascar	301	Perlmann <i>et al.</i> , 1994	54	2 to 35
Africa	Ethiopian Born (>7 years in Israel)	135*	Iancovici Kidon <i>et al.</i> , 2005	10	14.7±1.0
N.A.	North Carolina, U.S.A.	108	Buckley <i>et al.</i> , 1985	84	18-35
Europe	Croatia	107 <sup>c</sup>	Dodig <i>et al.</i> , 2006	7,975	0 to 16
M.E.	Ethiopian Israeli Born	54*	Iancovici Kidon <i>et al.</i> , 2005	15	6.4±2.3
Europe	Greek	54 <sup>c*</sup>	Petridou <i>et al.</i> , 1995	484	1 to 14
N.A.	U.S.A. (Multiple Ethnicities)	52	NHANES 2005-2006**	8,336	1 to 85
N.A.	Canada (only non-allergic)	12	Holford-Strevens <i>et al.</i> , 1984	1,814	20-65
Europe	Sweden (only non-atopic)	8	Perlmann <i>et al.</i> , 1994	38	not given

\* the published arithmetic mean was converted to geometric mean under the assumption of a lognormal distribution

using:  $G.M. = e^{\left(\ln(\bar{x}) + \frac{1}{2}\ln\left(1 + \left(\frac{\sigma^2}{\bar{x}^2}\right)\right)\right)}$  where  $\bar{x}$  is the arithmetic mean and  $\sigma$  is the standard deviation.

\*\* NHANES data calculated directly from NHANES data files at [www.cdc.gov/](http://www.cdc.gov/)

<sup>c</sup> Two or more reported groups were combined to form a single population estimate by converting to log IgE, calculating sample size weighted average log IgE and then converting back to geometric mean.

Region abbreviations: S.A. = South America, N.A. = North America, M.E. = Middle East

Table 2. Sample characteristics

		<b>0 to 7</b>		<b>8 to 15</b>		<b>Adults</b>	
		<b>F</b>	<b>M</b>	<b>F</b>	<b>M</b>	<b>F</b>	<b>M</b>
		<b>(n=32)</b>	<b>(n=31)</b>	<b>(n=37)</b>	<b>(n=25)</b>	<b>(n=21)</b>	<b>(n=16)</b>
Age (years)	Mean	5.66	5.97	10.59	10.52	38.46	43.43
	S.D.	1.64	1.61	2.18	1.25	10.59	13.99
Height (cm)	Mean	105.96	106.20	128.69	126.22	147.58	158.28
	S.D.	11.82	10.66	10.51	7.41	4.62	5.41
Weight (kg)	Mean	18.27	18.98	30.51	28.02	54.14	64.45
	S.D.	4.03	4.03	8.31	4.55	8.63	11.80
BMI	Mean	16.13	16.64	18.05	17.46	24.73	25.58
	S.D.	1.03	0.92	2.09	1.08	2.83	3.60
lnIgE (IU/ml)	Mean	6.92	7.14	7.24	7.66	6.48	6.97
	S.D.	1.00	1.00	1.03	0.55	0.82	0.98
IgE (IU/ml)	G. Mean	1,015	1,258	1,392	2,113	653	1,060
lnCRP (mg/ml)	Mean	7.43	7.39	7.06	7.14	7.03	6.91
	S.D.	0.76	0.97	0.78	0.93	0.66	0.59
CRP (mg/L)	G. Mean	1.68	1.62	1.16	1.26	1.13	1.00

Table 3. Regression of lnIgE and lnCRP on juvenile anthropometrics, with and without controlling for energy stores as indicated by skinfold thickness

	Ages	n	lnIgE		Sum4-SR		lnIgE x Sum4-SR		lnIgE x Older Age		
			$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	
Height-UR	0 to 7	63	.01	.99	-	-	-	-	-	-	
		48	-.50	.58	-1.82	.13	-	-	-	-	
		48	-.43	.64	-8.31	.44	.91	.55	-	-	
	8 to 15	61	-1.50	.05	-	-	-	-	-	-	
		61	-1.43	.05	1.76	<.01	-	-	-	-	
		61	-1.44	.05	-4.74	.26	.92	.12	-	-	
	0 to 15	125	-.75	.12	-	-	-	-	-	-	
		109	-1.18	.04	1.03	.05	-	-	-	-	
		109	-1.16	.05	-4.89	.24	.84	.15	-	-	
		125	-.01	.99	-	-	-	-	-1.51	.13	
		109	-.63	.48	1.05	.05	-	-	-.83	.48	
		109	-.56	.52	-4.90	.24	.84	.15	-.90	.44	
	Weight-UR	0 to 7	63	.22	.40	-	-	-	-	-	-
			48	-.17	.64	-.03	.95	-	-	-	-
48			-.17	.65	-.01	1.00	.00	1.00	-	-	
8 to 15		61	-.70	.21	-	-	-	-	-	-	
		61	-.63	.16	2.00	<.01	-	-	-	-	
		61	-.64	.13	-4.34	.08	.90	.01	-	-	
0 to 15		125	-.24	.40	-	-	-	-	-	-	
		109	-.51	.10	1.59	<.01	-	-	-	-	
		109	-.49	.10	-3.47	.11	.72	.02	-	-	
		125	.21	.58	-	-	-	-	-.92	.12	
		109	-.24	.60	1.60	<.01	-	-	-.40	.53	
		109	-.19	.68	-3.46	.11	.72	.02	-.46	.45	
BMI-UR		0 to 7	63	.05	.71	-	-	-	-	-	-
			48	-.01	.93	.49	.02	-	-	-	-
	48		-.04	.83	2.12	.26	-.23	.38	-	-	
	8 to 15	61	.04	.82	-	-	-	-	-	-	
		61	.06	.68	.64	<.01	-	-	-	-	
		61	.05	.69	-1.44	.07	.30	.01	-	-	
	0 to 15	125	.05	.64	-	-	-	-	-	-	
		109	.03	.79	.61	<.01	-	-	-	-	
		109	.03	.75	-.89	.22	.21	.04	-	-	
		125	.05	.74	-	-	-	-	-.01	.12	
		109	-.02	.90	.61	<.01	-	-	.08	.71	
		109	.00	.99	-.89	.22	.21	.04	.06	.79	
	Height-UR	0 to 7	63	-1.27	.07	-	-	-	-	-	-
			48	-1.45	.12	-1.89	.11	-	-	-	-
48			-1.35	.15	-10.83	.40	1.26	.49	-	-	
8 to 15		61	1.05	.21	-	-	-	-	-	-	
		61	1.29	.10	1.89	<.01	-	-	-	-	
		61	1.33	.10	-.16	.98	.30	.72	-	-	
All Ages		125	-.03	.96	-	-	-	-	-	-	
		109	.17	.79	1.04	.05	-	-	-	-	
		109	.19	.78	-.44	.94	.21	.79	-	-	
		125	-1.27	.09	-	-	-	-	2.32	.03	
		109	-1.40	.14	1.13	.03	-	-	2.59	.04	
		109	-1.38	.14	-.14	.98	.18	.81	2.60	.04	

Parameter values are in centimeters for height and kilograms for weight. Model terms not shown: Intercept, Age Group (bottom three models for each dependent variable). No significant relationships with lnIgE, either alone or in interaction, were found for Sum4-SR, and no significant relationships with lnCRP, either alone or in interaction, were found for Weight-UR, BMI-UR, or Sum4-SR (not shown).

Table 4. Regression of biomarkers on adult anthropometrics, controlling for age, sex, and skinfold thickness

Ind.	Dep.	B	SE	t	p	Partial $\eta^2$	Age (p)	Sex (p)	Sum4 (p)
lnCRP	Height (cm)	2.03	1.30	1.56	.13	.07	.22	<.01	-
	Weight (kg)	6.20	2.56	2.42	.02	.15	.58	.01	-
	BMI	2.00	.81	2.48	.02	.16	.91	.29	-
	Sum4 (mm)	9.76	5.23	1.86	.07	.11	.71	.01	-
	Height (cm)	.84	1.28	.66	.52	.07	.21	<.01	<.01
	Weight (kg)	2.46	1.73	1.43	.17	.07	.56	<.01	<.01
	BMI	.73	.51	1.42	.17	.07	.86	<.01	<.01
lnIgE	Height (cm)	-2.81	.85	-3.29	<.01	.26	.26	<.01	-
	Weight (kg)	-5.67	1.75	-3.24	<.01	.25	.58	<.01	-
	BMI	-1.59	.57	-2.80	<.01	.20	.87	.08	-
	Sum4 (mm)	-8.73	3.80	-2.30	.03	.15	.80	.04	-
	Height (cm)	-2.17	.90	-2.40	.02	.17	.26	<.01	.04
	Weight (kg)	-2.94	1.23	-2.40	.02	.17	.51	<.01	<.01
	BMI	-.58	.38	-1.54	.13	.08	.99	<.01	<.01

Models include the independent variable, intercept, age, and sex. For reference, the p-values for the age and sex control variables are shown. Models without Sum4 n=36, with Sum4 n=33. No significant interactions between either lnCRP or lnIGE and Sum4 were found (not shown).

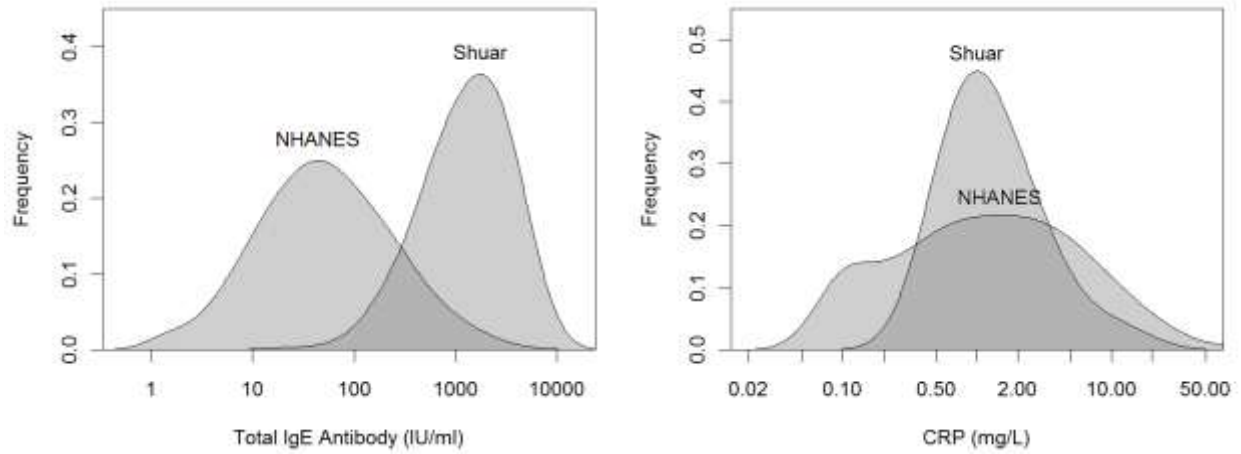


Fig. 1. Frequency distribution of Shuar IgE and CRP levels relative to NHANES 2005-2006.

Log-transforming IgE and CRP values largely corrects for the skew in untransformed values.

The density plots were generated with a Gaussian smooth and smoothing bandwidth of 0.5.

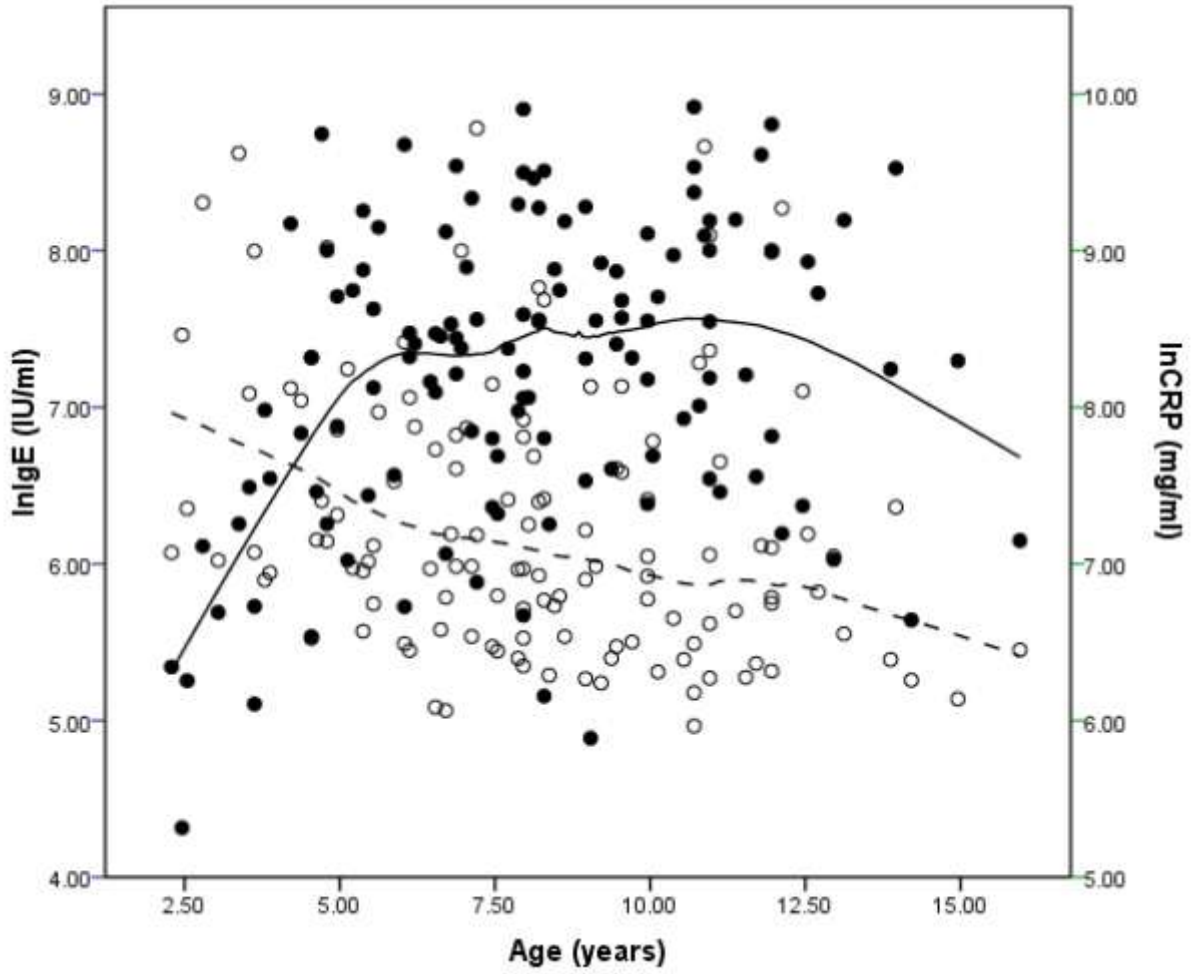


Fig. 2. Shuar age profiles of lnIgE (solid line, solid circles) and lnCRP (dashed line, open circles). Lines are triweight loess fit lines with a bandwidth of 0.5.

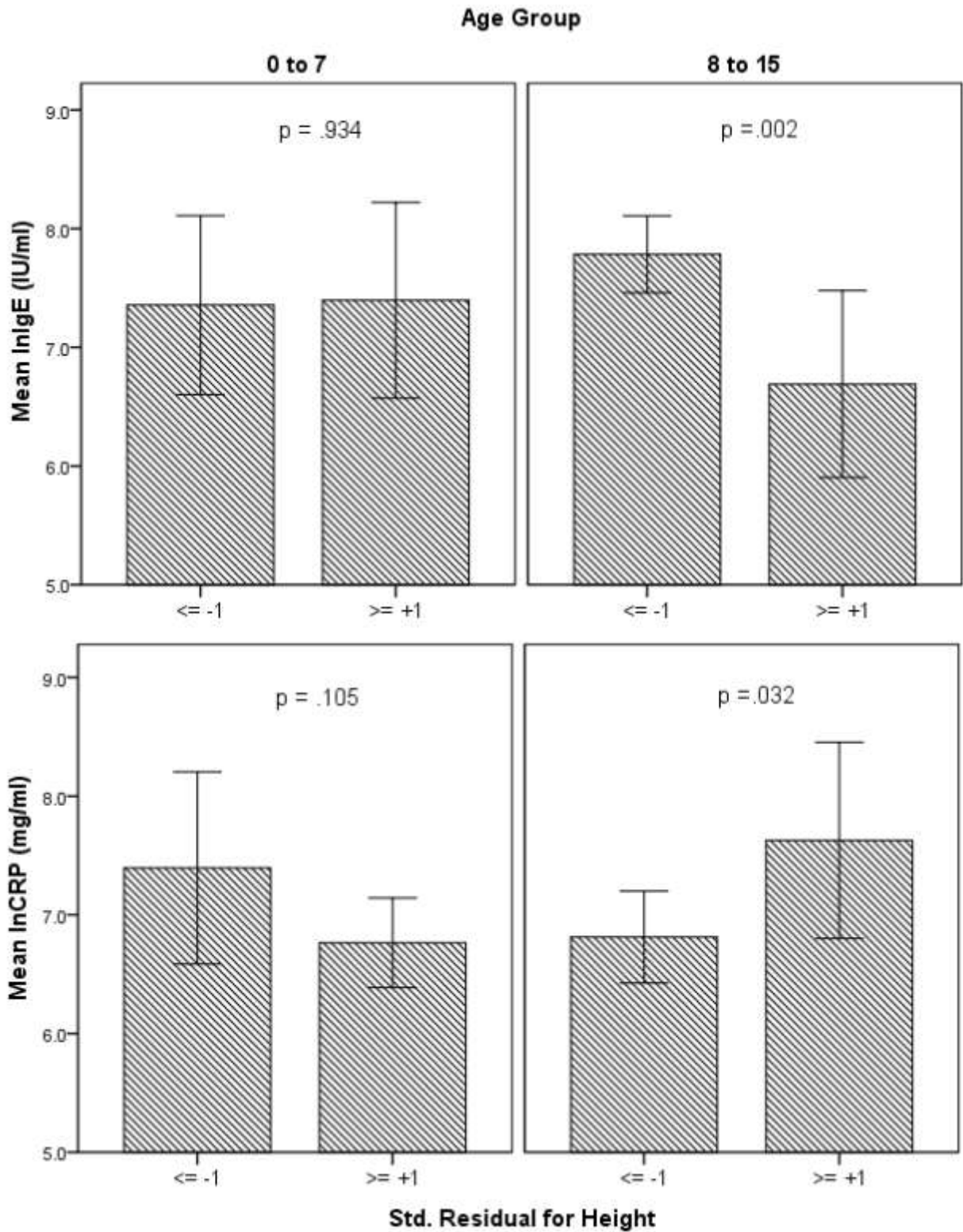


Fig. 3. Comparison of mean lnIgE and lnCRP in children more than one age-standardized residual above or below zero for height. Error bars are 95% confidence intervals for the mean.



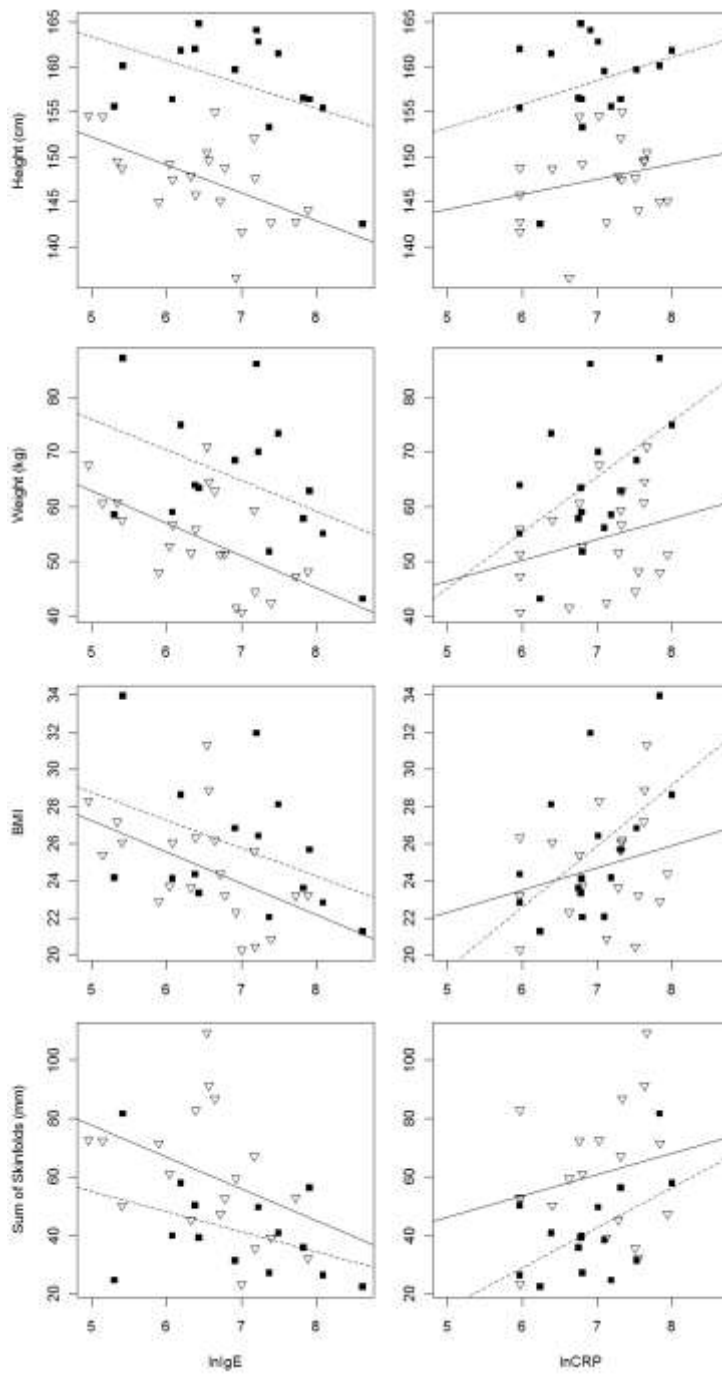


Fig. 4. Relationships between  $\ln IgE$  (left),  $\ln CRP$  (right) and anthropometrics in Shuar adults. Males are indicated with filled squares and dashed lines, females with open triangles and solid lines.