

Maintenance versus Growth: Investigating the Costs of Immune Activation Among Children in Lowland Bolivia

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ABSTRACT Immune function is a central component of maintenance effort, and it provides critical protection against the potentially life threatening effects of pathogens. However, immune defenses are energetically expensive, and the resources they consume are not available to support other activities related to growth and/or reproduction. In our study we use a life history theory framework to investigate tradeoffs between maintenance effort and growth among children in a remote area of Amazonian Bolivia. Baseline concentrations of C-reactive protein (CRP) were measured in 309 2- to 10-year olds as an indicator of immune activation, and height was

measured at baseline and three months later. Elevated CRP at baseline predicts smaller gains in height over the subsequent three months, with the costs to growth particularly high for 2- to 4-year olds and for those with low energy reserves (in the form of body fat) at the time of immunostimulation. These results provide evidence for a significant tradeoff between investment in immunity and growth in humans, and highlight an important physiological mechanism through which maintenance effort may have lasting effects on child growth and development. *Am J Phys Anthropol* 136:478–484, 2008.

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Life history theory begins with the premise that organisms attempt to allocate limited resources to primary life functions related to growth, reproduction, and maintenance in ways that optimize reproductive fitness (Stearns, 1992; Charnov, 1993). The immune system is an essential component of maintenance effort, playing central roles in cellular renewal and repair and in defending against the damaging—and potentially life threatening—effects of pathogenic agents (McDade, 2003). Immune defenses are energetically expensive, and resources consumed by immune processes are not available to support investments in activities related to growth and/or reproduction. Indeed, recent work in ecological immunology has highlighted the important roles that pathogen pressure and antipathogen defenses play in contributing to life history variation in a range of non-human populations (Sheldon and Verhulst, 1996; Lochmiller and Deerenberg, 2000). In our study we use a life history framework to investigate costs to growth associated with immune activation among children in a remote area of Amazonian Bolivia.

Attempts to evaluate life history tradeoffs in humans are challenged by the need to control for individual differences in resources that fuel investments in growth, reproduction, and maintenance. For example, children with reliable access to energy-rich foods will have sufficient fuel for growth as well as an effective immune response to infection, whereas relatively undernourished children will exhibit poorer growth and impaired immu-

nity. Simple correlations between growth and immune function may therefore reveal positive, rather than negative, associations between investments in growth and immune function. While the expected life history tradeoff still operates at the individual level (for all individuals, energy applied to immunity cannot also be allocated to growth), we may not see the tradeoff at the level of the population. This is the problem of phenotypic correlation (Hill and Hurtado, 1996).

A consideration of individual differences in phenotypic quality—both in terms of measurement and statistical analysis—is critical for a meaningful evaluation of life history tradeoffs in humans. In our study we attempt to address this issue by collecting data on a range of individual- and household-level factors that may shape phe-

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notypic quality, and by controlling for these factors in multivariate analyses. In addition, we explicitly evaluate individual differences in somatic energetic resources as a moderator of the association between immune activation and growth. In nutritionally marginal environments, fat stores represent critical supplies of energy upon which the body draws to fuel metabolic processes associated with growth as well as immune responses to infectious disease (Kuzawa, 1998). Individual differences in readily accessible energetic resources should therefore play a key role in defining the severity of life history tradeoffs associated with growth and immune function.

Detecting immune activation is an additional challenge for field-based research with humans. Clinical immune assessment protocols that require large volumes of blood and immediate access to laboratory facilities are not feasible in field settings, and symptom-based approaches typically used for research on infectious morbidity are subjective, vulnerable to under-reporting, and culturally variable (Martorell et al., 1975; Murray and Chen, 1992). In addition, they cannot detect subclinical infectious processes that may not manifest as observable symptoms, but that may nonetheless involve the activation of energetically costly antipathogen defenses (Rousham et al., 1998).

In our study, we use C-reactive protein (CRP) as a direct, objective measure of immune activation. CRP is the prototypical acute phase protein, and it functions as an important component of innate, nonspecific immune defenses involved in activating phagocytes and complement, and opsonizing bacteria, fungi, and parasites (Ballou and Kushner, 1992). Trace amounts of CRP are normally detectable in circulation, and concentrations increase by several orders of magnitude in response to a range of pathogens. CRP thus provides an indicator of infectious burden and degree of immunostimulation that is not sensitive to recall or reporting bias, and that can detect low levels of activation that may serve as a drain on energetic resources (Solomons et al., 1993; Rousham et al., 1998). Recent data from Nepal underscore the value of using acute phase proteins as objective measures of infection: Compared to children living in Kathmandu, village children had exceptionally high acute phase protein concentrations (as measured by α_1 -antichymotrypsin) despite reporting fewer symptoms of disease (Panter-Brick et al., 2000).

Monocytes and macrophages at the site of infection or tissue injury are primarily responsible for initiating the acute phase response. "Alarm" cytokines from the IL-1 and TNF families promote the release of a second wave of pro-inflammatory cytokines with local as well as systemic effects, including recruitment of leukocytes, initiation of a febrile response, and alterations in metabolism and acute phase protein production in the liver (Baumann and Gauldie, 1994). IL-6 is primarily responsible for upregulating hepatocyte production of CRP. Once released into circulation, the half-life of CRP is ~ 18 h and concentrations remain elevated during the course of infection for about one week following resolution (Gillespie et al., 1991). Concentrations of CRP above 5–10 mg/L have been associated with immunostimulation and symptoms of infectious disease (fever, cough, diarrhea, elevated white blood cell counts, positive blood cultures) in several field-based studies with infants, children, and adolescents (Doherty et al., 1993; Filteau et al., 1995; McDade et al., 2000; Campbell et al., 2003). The Tsimane'—a relatively isolated, indigenous Amazonian pop-

ulation in Bolivia—represent an excellent context in which to investigate life history tradeoffs associated with immune activation. In prior work we have documented high levels of growth stunting and infectious disease in this population, and we have investigated the cultural and economic determinants of child health (Foster et al., 2005; McDade et al., 2005; McDade et al., 2007). We expect that in this pathogen-rich environment, with relatively limited energetic resources, the costs of immune activation to child growth may be particularly high.

We sought to test three hypotheses based on prospective data collected from Tsimane' children at two time points, measured three months apart. First, activation of immune defenses at baseline will be associated with reduced gains in height over the subsequent three months. Second, the costs to growth of immune activation will be greater for younger children who are growing faster than older children, and who are more vulnerable to infectious disease because of the relative naiveté of their immune system (McDade, 2003).

Third, variation in energetic resources—in the form of body fat stores—will moderate the association between immune function and growth. In particular, we expected greater decrements in growth associated with immune activation in children with low energetic resources compared to children with high energetic resources. This hypothesis represents an explicit effort to model individual differences in phenotypic quality that may obscure significant life history tradeoffs.

METHODS

Study design

Research was conducted among the Tsimane', an Amazonian population of $\sim 8,000$ in the Department of Beni in Bolivia (Castillo, 1988; Riestler, 1993; Gullison et al., 1996; Godoy, 2001). Slash-and-burn farming is the primary means of subsistence, supplemented with hunting and gathering, wages labor in nearby logging camps or cattle ranches, or selling crops and forest goods. Data were collected as part of the ongoing Tsimane' Amazonian Panel Study, based in 13 communities that vary in distance from the town of San Borja (mean = 26.0 km, standard deviation = 16.7), the regional commercial center (population $\sim 19,000$). At the time of our study electricity and running water were not available to any household, and only half of the surveyed communities were accessible by road.

A baseline survey was conducted during May–August 2002, which included demographic, socio-economic, cultural, and health data, along with finger prick blood samples, and anthropometric measurements. Follow-up anthropometric measures and survey data were collected approximately 3 months later as part of a 1 year panel study with quarterly assessments. An attempt was made to recruit every resident of the 13 villages over the age of 2 years into the study. We limit our analyses to children between the ages of 2–10, inclusive, since it is during these years that children are most sensitive to growth faltering because of infection or undernutrition (Bogin, 1999). The study protocol was approved by the Northwestern University Institutional Review Board for research involving human subjects. The Tsimane' Grand Council also approved the study, and parental consent as well as child assent was obtained prior to enrollment.

Data collection

Primary caregivers provided information on household demographics, and economic activities and resources. Caregivers were also asked if their child had been sick over the preceding 2 weeks, as defined by the presence of symptoms of diarrhea or respiratory infection. Standard procedures (Lohman et al., 1988) were implemented to collect anthropometric measures of standing height (without footwear or hats) and weight (in light clothing). Sex-specific standardized scores for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) were calculated in EpiInfo (Version 3.2, CDC) using the CDC/WHO 1978 reference curves recommended for international use (World Health Organization, 1986). Subscapular, triceps, suprailiac, and abdominal skinfold thicknesses were measured to the nearest 0.5 mm with precision Lange calipers. The same researchers, using the same set of equipment, measured height at baseline and again 3 months later.

At least one drop of free flowing capillary blood was collected for analysis of CRP. Each participant's finger was cleaned with alcohol, and a sterile, disposable micro-lancet was used to deliver a controlled, uniform puncture. Whole blood was placed directly on standardized filter paper commonly used for neonatal screening (Whatman #903, Middlesex, UK). This relatively noninvasive blood collection protocol minimizes pain and inconvenience to the participants, and facilitates the collection of blood samples despite the constraints of field conditions (McDade et al., 2007). Samples were express shipped to Northwestern University and stored frozen at -30°C until analysis. Samples were exposed to tropical temperatures for less than 3 days, within the limits necessary to maintain sample integrity for CRP analysis (McDade et al., 2004).

Dried blood spot samples were analyzed for CRP in the Laboratory for Human Biology Research using an enzyme-linked immunosorbent assay (ELISA) protocol. Prior validation of assay performance indicates that the blood spot CRP method has good sensitivity, precision, and reliability, and a high correlation between matched plasma and blood spot samples (McDade et al., 2004). Sample concentrations were calculated from calibrators of known CRP concentration using the best fit 4-parameter logistic standard curve (KCJunior, BioTek). Between-assay coefficients of variation (SD/mean) for low and high control samples included with all runs were 7.9% and 9.0%, respectively.

Data analysis

Complete baseline anthropometric, CRP, and household data were available for 351 children, and follow-up growth data were available for 309. The 42 observations lost between baseline and the 3-month follow-up did not differ from the rest of the sample with respect to baseline height, CRP concentration, skinfold thickness, household wealth, or maternal characteristics, and are not included in any of the analyses below.

Statistical analyses were conducted with Stata for Windows, version 10.0 (StataCorp, College Station, TX). The dependent variable—gain in height over 90 days—was calculated by subtracting height at baseline from height measured approximately 3 months later, dividing by the number of days between measurements, and then standardizing to a 90 day period since not all height

measurements were taken precisely 90 days apart. We used 2 mg/L as a cut-off value to define children with low versus high concentrations of CRP. Prior analysis of matched plasma and blood spot samples (McDade et al., 2004) indicates that a blood spot CRP concentration of 2.0 mg/L is equivalent to ~ 3 mg/L plasma CRP. We chose a lower CRP concentration than is often used to identify infection since we are interested in exploring costs to growth associated with low-grade, subclinical levels of immune activation. However, in order to explore the possibility that costs to growth may be more severe at higher levels of immune activation, we also evaluated 3.0 and 4.0 mg/L as cut-off values for CRP.

To test the hypothesis that immune activation is associated with reduced growth, we investigated the association between elevated CRP at baseline and growth in height over the subsequent 3 months in a multivariate least squares regression model including age, gender, height at baseline, skinfold thickness, and household wealth. In preliminary analyses we evaluated a wider range of household measures of economic status, market integration, and acculturation, but none approached significance as predictors of height gain or as mediators of associations with CRP, and are therefore not discussed further. We included an interaction term between CRP elevation and age since we expected age to moderate the association between CRP and height gain; younger children grow faster, and are more vulnerable to infectious disease. We conducted these analyses for the entire sample, and then again for the subset of 2- to 4-year olds to investigate whether costs associated with immune activation were more severe in younger children.

To test our hypothesis that body fat serves as an energetic resource that moderates the impact of immune activation on growth; we added a term representing the interaction between CRP elevation and skinfold thickness at baseline. Skinfold thickness provides an estimate of the size of subcutaneous fat stores, which is directly related to total body fat (Gibson, 2005). Since skinfold thickness differs across gender and age groups, we used gender- and age-specific median values to categorize children into low or high skinfold group based on the sum of the four skinfold measurements.

The “cluster” option in Stata was specified for all models, with village designated as the clustering variable. This option relaxes the assumption that individual observations are independent, and requires only that observations be independent across clusters (Williams, 2000). This procedure adjusts for the fact that individuals were enrolled at the village level, and provides robust (and more conservative) estimates of variance around regression parameters.

Lastly, we applied a series of regression diagnostic procedures to assess the validity of our final models. Tests for linearity, homoscedasticity, outliers, and collinearity did not reveal problematic deviations from modeling assumptions.

RESULTS

On average, children gained 1.46 cm in height over 3 months, with 2- to 4-year olds growing substantially more than older children (Table 1). One in four children had concentrations of CRP greater than 2 mg/L at baseline, with 8- to 10-year olds least likely to have elevated CRP. Anthropometric measures of nutritional status indicate relatively high levels of stunting, but little evi-

TABLE 1. Descriptive statistics for 2- to 10-year old Tsimane' children (mean and (SD) for continuous variables)

	2-4 years	5-7 years	8-10 years	Total
N	93	119	97	309
Female (%)	51.6	46.2	41.2	46.3
Height-for-age (z)	-1.95 (1.11)	-1.81 (1.60)	-1.77 (1.06)	-1.84 (1.31)
Weight-for-age (z)	-0.97 (1.10)	-0.89 (1.38)	-0.95 (0.78)	-0.93 (1.13)
Weight-for-height (z)	0.29 (1.02)	0.34 (0.91)	0.60 (0.58)	0.39 (0.88)
Height gain (cm)	1.91 (1.15)	1.40 (0.91)	1.11 (0.83)	1.46 (1.01)
Sum of four skinfolds (mm)	24.8 (6.7)	22.4 (5.2)	23.7 (6.8)	23.5 (6.3)
CRP ≥ 2 mg/L (%)	29.0	28.6	14.4	24.3

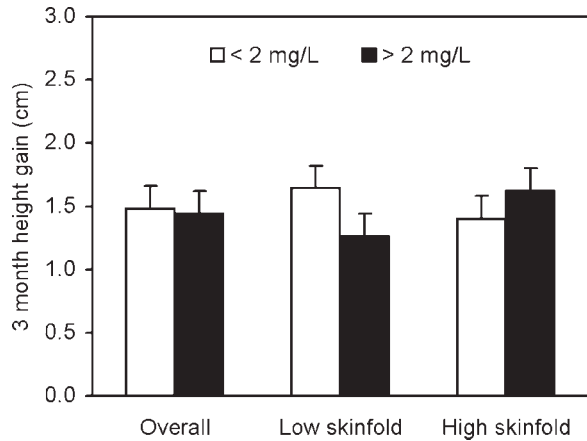


Fig. 1. Association between immune activation and three month height gain (mean ± S.E.) for the entire sample of 2- to 10-year old Tsimane' children, and stratified by skinfold thickness at baseline (based on coefficients in Table 2).

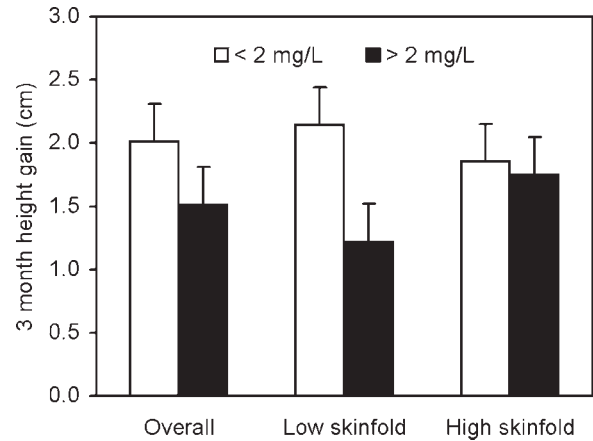


Fig. 2. Association between immune activation and three month height gain (mean ± S.E.) for all 2- to 4-year old Tsimane' children, and stratified by skinfold thickness at baseline (based on coefficients in Table 2).

dence of wasting, similar to other Amazonian populations (Foster et al., 2005). There were no gender differences in height gain or CRP concentrations, nor any evidence of significant gender interactions.

Among children with CRP >2 mg/L, 70.4% reported symptoms of infectious disease in the preceding two weeks, compared to 50.7% of children with CRP ≤2 mg/L. Among those with symptoms of infection, 29.6% had elevated CRP, compared to only 16.1% of those not reporting infectious symptoms (Pearson $\chi^2 = 6.89, P < 0.01$). This pattern of results suggests that CRP concentrations are significantly related to infectious disease in this population, although this association is far from one-to-one most likely due to individual variation in reporting of symptoms, and due to the fact that CRP concentrations may be elevated in the absence of overt symptoms.

In the entire sample of 2- to 10-year olds, elevated CRP at baseline was not significantly associated with height gain over the subsequent 3 months: Controlling for covariates in our regression model, children with elevated CRP grew on average 1.44 cm, compared to 1.48 cm for those with low CRP (see Fig. 1). In contrast, elevated CRP was associated with significant costs to growth for 2- to 4-year olds: Young children with elevated CRP at baseline gained 1.51 cm in height, compared to 2.01 cm for children with low CRP at baseline (see Fig. 2).

We next tested hypothesis two, that individual differences in energetic resources moderate the association between immune activation and growth. For the entire sample, there was a statistically significant interaction

between CRP status and skinfold thickness in predicting 3 month height gain (Table 2). For children with skinfold thickness below the age- and sex-specific sample median, high CRP was associated with a 0.38 cm reduction in height gain relative to children with low CRP (see Fig. 1). For those with high skinfold thickness, elevated CRP was not associated with reduced growth, and was in fact associated with a slight increase in height gain.

Skinfold thickness also moderated the association between immune activation and growth in younger children, with larger decrements in height evident in 2- to 4-year olds. For young children with low skinfold thickness at baseline, elevated CRP was associated with a 0.92 cm reduction in height gain relative to children with low CRP (see Fig. 2). For those with high skinfold thickness, the reduction in height gain associated with elevated CRP was 0.10 cm.

Similar, though weaker, associations with height gain were obtained with different cut-off values for CRP. For example, 2- to 4-year olds with CRP >3.0 mg/L gained 0.30 cm less than those with CRP ≤3 mg/L, compared to a difference of 0.51 cm when 2 mg/L was used as our cut-off. For children of all ages with low skinfold thickness, CRP >3.0 mg/L was associated with a relative loss of 0.18 cm in height gain, compared to 0.38 cm with 2 mg/L as the cut-off value. Low numbers of individuals with CRP >4 mg/L (N = 39) precluded analyses with this cut-off value, particularly given the significance of interactions with age and skinfold thickness. Since the number of individuals with CRP >3 mg/L was also not high (N = 53), it is difficult to determine whether the weaker associations with height gained compared to the

TABLE 2. Ordinary least squares regression model predicting three month height gain (cm) in the entire sample of 2- to 10-year olds (model $R^2 = 0.145$, $P < 0.0001$), and in the subset of 2- to 4-year olds (model $R^2 = 0.151$, $P < 0.01$)

Variable	2- to 10-year olds			2- to 4-year olds		
	B	SE	P-value	B	SE	P-value
CRP \geq 2 mg/L	-1.35	0.29	0.001	-0.92	0.27	0.006
Skinfold > median	-0.36	0.86	0.001	-0.29	0.19	0.150
CRP \times skinfold	0.74	0.25	0.011	0.80	0.25	0.008
Age (yrs)	-0.12	0.04	0.017			
CRP \times age	0.16	0.04	0.002			
Female	-0.01	0.10	0.943	-0.10	0.23	0.679
Baseline stature (cm)	-0.01	0.01	0.440	-0.02	0.01	0.199
Household wealth (quintiles)	0.05	0.03	0.099	0.20	0.09	0.039
Constant	2.91	0.68	0.001	3.46	1.37	0.027

Age and the interaction term for CRP \times age are not included in the model for 2- to 4-year olds due to the limited age range.

2 mg/L cut-off value are because of lack of statistical power, or because the lower cut-off value is more effective at capturing chronic, low-grade immunostimulation.

DISCUSSION

In our study we find evidence for a significant life history tradeoff between investment in maintenance versus growth: For 'Tsimane' children, activation of immune defenses predicts smaller gains in height over the subsequent three months. This cost to growth is particularly high for young children, and for those with low energy stores at the time of immunostimulation.

These costs are substantial. Children between the ages of 2- to 4-years can expect to grow 7 or 8 cm/year (Bogin, 1999). If short-term growth deficits due to immune activation are not recovered through a subsequent bout of catch-up growth, young 'Tsimane' children with low body fat stores may lose 10–15% of their expected annual height gain. These losses can have significant fitness implications: stunted growth is associated with reduced work capacity and poorer reproductive outcomes in adulthood, as well as increased mortality risk (Martorell, 1989). Undernutrition and infectious disease are common in much of the developing world (World Health Organization, 1998; de Onis et al., 2004), and these analyses underscore the potential costs of immune activation in resource poor settings that may have long term implications for health.

These findings are consistent with experimental animal models that have demonstrated costs to survival, reproduction, and/or growth resulting from immune activation (Buttgereit et al., 2000; Read and Allen, 2000; Martin et al., 2002). They are also consistent with the well-established negative effects of infection on child growth (Martorell et al., 1975; Scrimshaw, 1981), but they go beyond in using CRP as a measure of immune activation. The direct energetic costs of immunity are difficult to isolate since infections initiate other processes that may affect growth, including loss of appetite, anorexia, and impaired nutrient absorption (Gershwin et al., 2000). While we cannot eliminate these factors as contributing to growth faltering in this study, CRP provides a direct physiological measure of immune activation that identifies low levels of activity that are not likely to be associated with overt symptoms of infectious disease, but that nonetheless tap into energetic resources that would otherwise be available for growth. As such we have a more sensitive measure of immune activation

that we link prospectively to deficits in height gain.

Phenotypic correlations are a significant challenge for within-species analyses of life history variation. This is particularly true for research with humans, where there may be large differences in access to resources (or efficiency in their use), and where experimental protocols that attempt to manipulate—or eliminate—these differences are not feasible. Simple bivariate, correlational analyses are not likely to yield compelling evidence for significant life history tradeoffs in humans. Instead, population-based approaches that collect data on a wide range of factors that may obscure life history tradeoffs are likely to prove more productive.

Our analyses demonstrate the value of such an approach. For 2- to 4-year olds, simple bivariate comparisons estimate the growth costs of immune activation to be 0.42 cm. Multivariate analyses allowed us to control for the independent effects of attributes related to nutritional status and household wealth. Adjusting for these factors, the estimated cost to growth increased to 0.50 cm. However, these costs were not distributed equally across all 2- to 4-year olds: The cost to growth for young children with low body fat stores was 0.92 cm, while it was only 0.10 cm for those with high body fat. By accounting for individual differences in energetic resources we were able to reveal the high growth cost of immune activation for a subset of children. This final result underscores the importance of drawing on clearly specified conceptual models that include plausible causal pathways to adequately test hypotheses derived from life history theory.

It is worth commenting on the apparently negative association between baseline skinfold thickness and subsequent gain in height reported in Table 2. This association is counter to expectation, but we have determined that it is the result of including an interaction term with CRP. On the basis of the regression coefficients reported in Table 2, children with high skinfold thickness at baseline grew on average 1.51 cm, compared to 1.45 cm for children with low skinfolds. For 2- to 4-year olds, children with high skinfold thickness grew on average 1.80 cm, compared to 1.68 cm for children with low skinfolds. This pattern of results is consistent with prior research linking energy stores positively with linear growth, although the differences are not as large as one might expect. This issue is worthy of additional consideration, and may reflect complex dynamics between body fat stores and linear growth.

A major strength of this study is the prospective design, which increases our confidence in concluding that immune activation at baseline is causally related to deficits in height gain over the subsequent three months. However, it is possible that other unmeasured factors correlated with elevated CRP are actually contributing to poor growth, despite our efforts to consider a wide range of variables representing attributes of the household environment. Another limitation is our use of a single CRP measurement, which does not allow us to determine whether a child with elevated CRP is suffering from chronic, low grade immunostimulation, or is in the recovery phase following acute activation of anti-pathogen defenses. Both consume energetic resources with potential implications for growth, but subsequent research with more frequent blood sampling, and with larger sample sizes, will be required to differentiate these processes in order to evaluate the patterns and levels of immune activation that have the strongest consequences for growth.

Immune function is central to maintenance effort, and explicit consideration of investment in antipathogen defenses in human populations inhabiting diverse ecologies may reveal physiological mechanisms underlying life history tradeoffs, and provide insight into variation in human life history strategies. Similarly, an adaptationist, ecological approach to studying human physiology and health complements the cellular and molecular perspectives that predominate in the biomedical sciences, and suggests novel hypotheses and interpretations that cast new light on variation in human immune function, growth, and health.

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