

# Adrenal maturation, nutritional status, and mucosal immunity in Bolivian youth

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## Abstract

**Objectives:** Humans—and several other apes—exhibit a unique pattern of post-natal adrenal maturation; however, the causes and consequences of variation in adrenal development are not well understood. In this study, we examine developmental and age-related maturation of the adrenal gland (measured via dehydroepiandrosterone-sulfate [DHEA-S]) for potential life-history associations with growth and mucosal immunity in a rural population of immune-challenged Bolivian juveniles and adolescents.

**Methods:** Salivary DHEA-S, anthropometrics, and salivary mucosal immunity (secretory IgA [sIgA]) were measured in 171 males and females, aged 8–23.

**Results:** Males with greater energy (i.e. fat) stores showed higher DHEA-S levels. Controlling for age and energetic condition (to control for phenotypic correlation), higher DHEA-S was associated with higher mucosal immunity (sIgA) among both males and females. Higher DHEA-S levels were positively associated with growth (i.e. height and strength) in males.

**Conclusions:** In accordance with predictions derived from life-history theory, males with higher energy stores secrete more adrenal androgens. This suggests that adrenal maturation is costly and subject to constraints; that is, only males with sufficient reserves will invest in accelerated adrenal maturation. Further, DHEA-S appears to have a measurable influence on immunocompetence in adolescent males and females; therefore, deficits in DHEA-S may have important consequences for health and maturation during this period. Adrenal maturation is an important, but understudied component of human growth and development.

## 1 | INTRODUCTION

A life-history perspective posits that selection favors efficient mechanisms that allocate finite energy and material stores to competing physiological demands, trading-off between investments in growth, survival/maintenance, and reproduction (Hill, 1993; Kaplan, Hill, Lancaster, & Hurtado, 2000; Stearns, 1992). Investment in survival includes (but is not limited to) distribution of energy to immune functioning (McDade, 2003; Muehlenbein & Bribiescas, 2005) and its subcomponents (McDade, Georgiev, & Kuzawa, 2016),

whereas competing investments in growth and reproduction may include energetic allocation to physical development, such as height and muscle mass (Andersson, 1994). Given constraints, optimal energy allocation to different demands varies across the life course, and the shift from one life-history stage to the next involves alterations in energy allocation “decisions” (Hill, 1993; Kaplan et al., 2000; Stearns, 1992).

Research indicates that the timing of puberty (ie gonadarche) depends in part on energy status (Bogin, 1999; Ellison, 2003; Ellison et al., 2012; Lassek & Gaulin, 2007;

Pozo & Argente, 2002; Walker et al., 2006), and that this may be true for adrenarche as well (Coutinho et al., 2007; Leenstra et al., 2003). Around 6–8 years of age (Campbell, 2011; Kroboth, Salek, Pittenger, Fabian, Frye, 2011), the adrenal gland secretes increasing levels of the androgens dehydroepiandrosterone and its sulfate version (DHEA-S). DHEA-S acts as a reservoir for DHEA, but the two hormones are interconvertible, often treated as interchangeable, and have similar effects in some contexts through a variety of mechanisms (Dong and Zheng, 2012; Longscope, 1996; Starka et al., 2015; Webb et al., 2006) DHEA-S increases in conjunction with the maturation of the zone reticularis of the adrenal cortex (Havelock, Auchus, & Rainey, 2004). This developmental event appears to have no consistent effect on the timing of gonadarche; those with premature or delayed adrenarche may have normal gonadarche and vice versa (Palmert et al., 2001). The zona reticularis continues to develop throughout adolescence, with DHEA-S levels reaching their peak in early adulthood (Orentreich, Brind, Rizer, & Vogelmann, 1984). Thus, adrenal maturation continues beyond 8 years of age, and individuals vary in the amount and rate of DHEA-S secretion throughout development (Granger, Schwartz, Booth, Booth, & Zakaria, 1999; Ibáñez, Potau, Marcos, & de Zegher, 1999; Palmert et al., 2001).

Little is known about the causes and consequences of variation in this developmental sequence, and in particular the role of energy deficits or disease ecology in explaining individual differences. We suggest that these environmental inputs may shape juvenile and adolescent phenotypic development via adjustment in adrenal androgen secretion. Life-history theory has proven a useful framework for understanding variation in the timing of gonadal puberty (eg Belsky et al., 2007; Cameron, 2007; Walker et al., 2006). Therefore, in this study, we apply a life-history perspective to understand variation in adrenal development by examining the relationships between adrenal maturation and 3 life-history parameters: overall energy budgets, immune function, and growth.

First, we ask whether adrenal development is subject to energetic constraints. Several sources of evidence suggest that energetic status is communicated to the adrenal gland. For instance, the adrenal cortex expresses receptors for insulin and insulin-like growth factor (IGF-1; Fottner, Engelhardt, & Weber, 1998). Further, leptin, a hormone secreted by adipocytes, has a stimulating effect on 17- $\alpha$ -hydroxylase and 17- $\beta$ -lyase, critical enzymes for the synthesis of adrenal androgens (Biaison-Lauber, Zachmann, & Schoenle, 2000). The empirical relationship between measures of body fat and adrenal androgens, however, shows conflicting results (Nestler, Barlascini, Clore, & Blackard, 1988; Perrini et al., 2004; Remer and Manz, 1999; Tagliaferro, Davis, Truchon, & Van Hamont, 1986; Tchernof & Labrie, 2004; Villareal & Holloszy, 2004).

As a second step, we examine the relationship between adrenal maturation and immune investment. DHEA/S plays

an important role in multiple physiological systems. As a precursor hormone for the synthesis of sex steroids, DHEA/S may be viewed as an important facet of reproductive development. Conversely, DHEA/S is well studied for its role in healthy growth and aging, particularly from the perspective of immunocompetence.

In the present analysis, we use a measure of mucosal immunity, secretory IgA (sIgA). As the dominant immunoglobulin on all mucosal surfaces, sIgA acts as a first line of defence against invading pathogens in the oral and nasal cavities, respiratory system, gastrointestinal tract, and genitourinary tract (Brandtzaeg, 2009). Although the relationship between sIgA and other sex steroids (i.e. T) has been studied with conflicting results (Gettler, McDade, Agustin, Feranil, & Kuzawa, 2014; Van Anders, 2010), research on the relationship between DHEA/S and sIgA concentrations in human saliva is lacking.

Finally, we explore the relationship between adrenal maturation and physical (i.e. skeletal and muscular) growth. During puberty, androgens (including testosterone and DHEA/S) play a role in both skeletal (Cassorla et al., 1984; Preece et al., 1984) and muscular development (Arquitt, Stoecker, Hermann, & Winterfeldt, 1991). Higher DHEA/S is associated with enhanced osteoblastic cell differentiation (Scheven & Milne, 1997) and strengthening of the bone (Remer et al., 2003), as well as elevated levels of IGF-1 (Fottner et al., 1998; Smith et al., 1989). Few studies, however, have addressed population-level relationships between DHEA/S and growth (cf. Zemel & Katz, 1986). Adrenal maturation and the elevation of adrenal androgens in particular, tie together these important life-history traits. Understanding how DHEA-S mediates the allocation of energy to immunity and growth may shed light on the evolutionary role of adrenal androgens during this formative stage of development. Additionally, intersections in development, DHEA-S, and mucosal immunity are poorly studied in humans, and even less so in populations of anthropological interest, where energetic stresses and high pathogen loads converge to create tighter energy budgets. In accordance with life history theory and the empirical literature, we make the following predictions for the present research:

1. If adrenal maturation is constrained by energy availability, individuals with greater energy budgets (as evidenced by larger height-controlled fat stores) will exhibit greater investment in adrenal maturation (as manifested by higher DHEA-S levels). This relationship should remain after controlling for age, because the pacing of development will vary among individuals of the same age.
2. Because the empirical literature suggests that juvenile and adolescent DHEA-S may be viewed as investment in maintenance, individuals with higher DHEA-S (and,

similarly, those with higher energy availability) should show elevated mucosal immunity. This relationship should remain after controlling for differences in age and overall energy budget (to adjust for phenotypic correlations).

3. The empirical literature suggests that DHEA-S may also stimulate growth, therefore we predict a positive relationship between DHEA-S and height and/or strength (controlling for age and phenotypic correlation).
4. Life history theory further predicts that immunity and growth trade-off (McDade, 2003; Muehlenbein & Bribiescas, 2005), such that Tsimane juveniles and adolescents with substantial investment in immunity may show deficits in height and strength. Given the predicted positive association between DHEA-S and both growth and immunity, DHEA-S—like body fat—may itself measure phenotypic correlation, and controlling for it may draw forth growth-immunity trade-offs. Therefore we predict an inverse association between sIgA and height and/or strength after controlling for energetic status and DHEA-S.

## 2 | METHOD

### 2.1 | Population

The Tsimane are forager-horticulturalists residing in the lowland Amazonian forests of central Bolivia (Gurven, Kaplan, & Supa, 2007; Gurven, Kaplan, Winking, Finch, & Crimmins, 2008). The Tsimane experience an immune-taxing environment, with high rates of infection (Vasunilashorn et al., 2010), gastrointestinal and respiratory disease (Gurven et al., 2008), and anemia (Vasunilashorn et al., 2010). A number of measures of immunity are chronically elevated in Tsimane, including leukocytes, and serum immunoglobulins (Blackwell et al., 2016). In addition, living conditions are more energetically demanding than in the developed world, characterized by higher workloads, variable food supply and medical access, and no sanitation or water treatment infrastructure.

### 2.2 | Participants

Height and weight were collected from 90 males (age range 8–23;  $M \pm SD = 13.7 \pm 3.4$ ) and 81 non-pregnant females (age range 8–17;  $M \pm SD = 13.5 \pm 3.2$ ). Of these, 80 males and 74 females contributed one 2 mL saliva sample. Breast-feeding mothers ( $N = 14$ ) were excluded from analyses due to the immune and endocrine changes that occur with breast-feeding. All data were collected in accordance with procedures approved by the Institutional Review Board at the University of California, Santa Barbara.

### 2.3 | Saliva collection

No participant had eaten in the hour before testing; nevertheless, participants were asked to rinse their mouth with clean water in order to mitigate contamination from food, drink, and blood (Vitzthum, von Dornum, & Ellison, 1993) before filling a 2 mL polystyrene cryotube with bubble-free saliva by passive drool. Saliva collection time was recorded in order to calculate salivary flow rate (i.e. the volume of saliva excreted in a given unit of time), which affects both sIgA and DHEA-S (Kugler, Hess, & Haake, 1992; Miletic, Schiffman, Miletic, & Sattely-Miller, 1996). Samples were stored in a liquid nitrogen tank and then transported on dry ice to University of California, Santa Barbara where they remained frozen (at  $-80^{\circ}\text{C}$ ) for approximately 6 months. They were then shipped on dry ice and then assayed by Salimetrics Laboratory. For additional details on saliva collection, see Hodges-Simeon, Gurven, and Gaulin (2015).

### 2.4 | Endocrine and immune assays and data treatment

#### 2.4.1 | Dehydroepiandrosterone-sulfate

All assays were completed in duplicate with a highly sensitive competitive enzyme immunoassay (EIA) protocol by Salimetrics LLC (State College, PA; catalog #1–1252). Plasma DHEA-S is significantly correlated with salivary DHEA-S (Jezova & Hlavacova, 2008). However, unlike DHEA, DHEA-S does not directly diffuse into saliva so concentrations are dependent on salivary flow (Vining, McGinley, & Symons, 1983) and final measurements must be corrected for flow rate (Kugler et al., 1992; Miletic et al., 1996). Flow rate is the volume of the saliva divided by the time to produce it (current sample:  $M = 0.22$  mL/minute,  $SD = 0.16$ ). Original concentrations of the analyte were multiplied by flow rate (mL/min) in order to express results as a secretion rate (i.e. output per unit of time), and all results presented here reflect this correction. Transferrin levels were also tested to address potential blood contamination (see Section 2.6 below). Although results are somewhat inconsistent, most studies show that DHEA-S exhibits little diurnal rhythm (Rosenfeld, Rosenberg, Fukushima, & Hellman, 1975). In the present sample, DHEA-S was not correlated with sample collection time. The average intra-assay and inter-assay coefficients of variation were 7.3% and 7.6%. The lower limit of sensitivity was  $<43$  pg/mL. The standard curve range was 188.9–15,300 pg/mL.

#### 2.4.2 | Secretory IgA

Salimetrics EIAs were also used to assay concentrations of sIgA according to standard procedures (catalog #1–1602).

**TABLE 1** Correlations among variables for males (lower left triangle)

	DHEA-S (pg/mL)	sIgA (μg/mL)	Adiposity	BMI-R	Age (years)	Height (cm)	Strength
DHEA-S	...	0.57***	0.16	0.26*	...	0.27*	0.39**
sIgA	0.64***	...	0.09	0.07	...	0.19	0.13
Adiposity	0.29*	0.16	...	0.54***	...	0.39***	0.48***
BMI-R	0.24*	0.08	0.54***	...	...	0.36**	0.58***
Age	0.56***	0.34**	0.27*	0.04	...	...	...
Height	0.60***	0.38**	0.42***	0.22†	0.86***	...	0.79***
Strength	0.65***	0.35**	0.45***	0.34**	0.86***	0.94***	...
Males							
Mean	1143.38	25.61	14.55	...	13.44	144.91	...
SD	1094.49	21.73	2.98	...	3.33	15.55	...

Age-controlled partial correlations in upper right triangle. Descriptive statistics above.

Note. DHEA-S, dehydroepiandrosterone-sulfate; sIgA, secretory IgA; BMI-R, Tsimane-specific BMI-for-age residuals; SD, standard deviation. Correlations use log-transformed variables (when appropriate); however, means and standard deviations are derived from unmodified data.

† $P < .10$ , \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

sIgA is not directly related to serum IgA (Brandtzaeg, 2007), and like DHEA-S, is sensitive to salivary flow rate and is appropriately analyzed as a secretion rate (Kugler et al., 1992; Miletic et al., 1996). In all results presented below, sIgA refers to the salivary-flow-corrected rate. The average intra-assay and inter-assay coefficients of variation were 5.6% and 8.8%. The lower limit of sensitivity was 2.5 μg/mL. The standard curve range was 2.5 μg/mL to 600 μg/mL. Like DHEA-S, sIgA was not correlated with sample collection time.

## 2.5 | Growth and energetic status

Standard anthropometric protocols were used to assess growth and energetic status (Lohman, Roche, & Matorell, 1988); participants wore light clothing and no shoes for measurement. We utilize 2 measures of current energy reserves. First, an adiposity equation (Slaughter et al., 1988) was used to estimate fat stores for males and females based on tricep, suprailiac, and subscapular skinfolds, which were measured on the right side in duplicate to the nearest 0.2 mm using a Harpenden caliper. Second, age-standardized residuals were calculated for body mass index (BMI) separately for males and females using Tsimane- and sex-specific BMI-for-age curves (BMI-R; Blackwell et al., 2017; Urlacher et al., 2016). These 2 measures produced very similar results in the multiple regression models below; therefore, for simplicity, we primarily report results for the models using BMI-R. Grip strength was measured using a Baseline bulb pneumatic hand dynamometer to the nearest 0.5 psi. This measure was standardized and summed with standardized flexed

bicep size (Puts, Apicella, & Cárdenas, 2012; Sell et al., 2009), which was recorded to the nearest 0.2 cm using an anthropometric tape measure.

## 2.6 | Data analysis

Means and SDs for unmodified variables are found in Tables 1 and 2. Log<sub>10</sub> transformations were applied to normalize data distributions for DHEA-S, sIgA, age, height, and strength for use in regression analysis. Other variables were normally distributed (Shapiro-Wilk,  $P > .05$ ). For all multiple regression models, variance inflation factors were small. Outliers >3 SDs above the mean for transferrin ( $N = 3$ ) were removed from the analyses. Final sample size after exclusions was 77 males and 60 females. Further, time of day and flow rate—both potential confounds—were included and subsequently removed from all multiple regression models because they produced only trivial alterations from the original models.

## 3 | RESULTS

### 3.1 | Sex differences

Point-biserial correlations were used to identify sex differences in the variables of interest. DHEA-S ( $r = 0.32$ ,  $P < .001$ ), sIgA ( $r = 0.25$ ,  $P < .01$ ), and adiposity ( $r = -0.66$ ,  $P < .001$ ) were significantly correlated with sex (females coded “0”); however, height ( $r = 0.10$ ,  $ns$ ), and strength ( $r = -0.03$ ,  $ns$ ) were not (due to the mixed age sample). BMI-R ( $r = -0.03$ ,  $ns$ ), which already takes age and

**TABLE 2** Correlations among variables for females (lower left triangle)

	DHEA-S (pg/mL)	sIgA (μg/mL)	Adiposity	BMI-R	Age (years)	Height (cm)	Strength
DHEA-S	...	0.50***	-0.13	-0.08	...	0.06	-0.08
sIgA	0.54***	...	-0.02	-0.12	...	0.29*	0.10
Adiposity	0.11	-0.03	...	0.61***	...	0.40**	0.52***
BMI-R	-0.08	-0.15	0.55***	...	...	0.34*	0.63***
Age	0.25*	-0.02	0.73***	0.17	...	...	...
Height	0.27*	0.17	0.74***	0.31*	0.80***	...	0.69***
Strength	0.16	0.01	0.82***	0.49***	0.86***	0.89***	...
Females							
Mean	579.58	18.23	22.50	...	12.27	141.64	...
SD	1042.21	14.04	6.04	...	2.16	10.53	...

Age-controlled partial correlations in upper right triangle. Descriptive statistics above.

Note. DHEA-S, dehydroepiandrosterone-sulfate; sIgA, secretory IgA; BMI-R, Tsimane-specific BMI-for-age residuals; SD, standard deviation. Correlations use log-transformed variables (when appropriate); however, means and standard deviations are derived from unmodified data. Strength and BMI-R are standardized measures; therefore, descriptive statistics are not included.

† $P < .10$ , \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

sex into account, was also uncorrelated, suggesting that it is an appropriate control in subsequent analyses. Due to the presence of sex differences, we analyzed males and females separately in all the following analyses. Descriptive statistics for all variables of interest may be found in Tables 1 (males) and 2 (females).

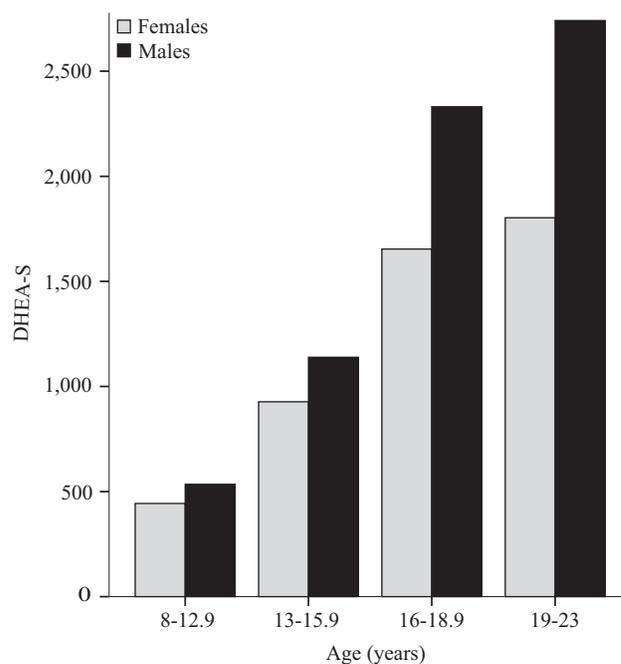
### 3.2 | Age-related variation

For males, a significant relationship existed between age and DHEA-S ( $r = 0.56$ ,  $P < .001$ ), sIgA ( $r = 0.34$ ,  $P < .01$ ), adiposity ( $r = 0.27$ ,  $P < .05$ ), height ( $r = 0.86$ ,  $P < .001$ ), and strength ( $r = 0.86$ ,  $P < .001$ ), but not BMI-R ( $r = 0.04$ ,  $ns$ ). For females, age was significantly correlated with DHEA-S ( $r = 0.25$ ,  $P = .05$ ), adiposity ( $r = 0.73$ ,  $P < .001$ ), height ( $r = 0.80$ ,  $P < .001$ ), and strength ( $r = 0.86$ ,  $P < .001$ ), but not sIgA ( $r = -.02$ ,  $ns$ ) nor BMI-R ( $r = 0.17$ ,  $ns$ ). See Tables 1 and 2 for linear correlations. See also Figure 1 for DHEA-S (untransformed) for different age groups in males and females. Age is more strongly correlated with DHEA-S in males than in females (Fisher's  $z = 2.14$ ,  $P < .05$ ). Because of these age-related changes, the following analyses control for age. In doing so, we address developmental relationships between the variables of interest rather than those simply due to age-related trends.

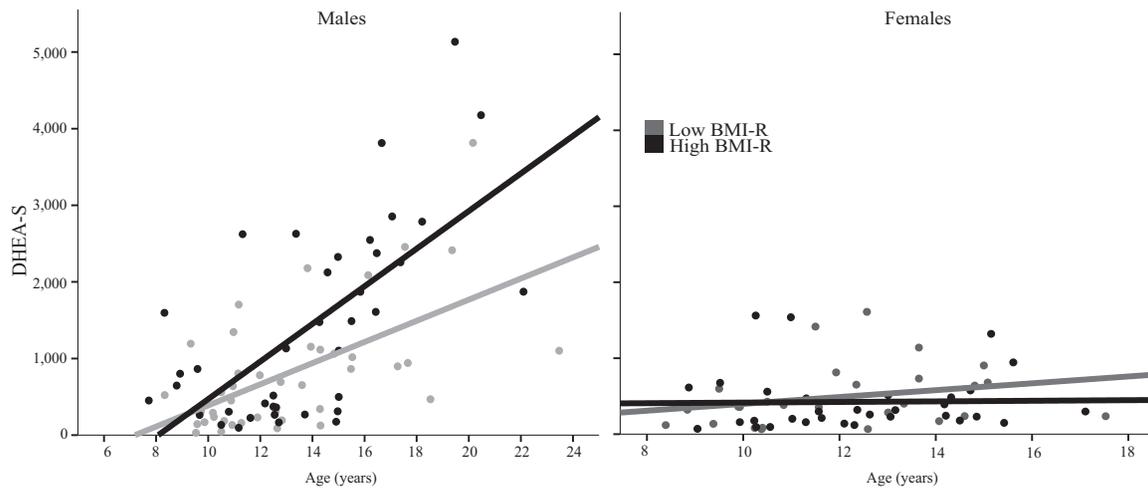
### 3.3 | Is adrenal maturation subject to energetic constraints?

In males, DHEA-S is significantly correlated with adiposity ( $r = 0.29$ ,  $P < .05$ ) and BMI-R ( $r = 0.24$ ,  $P < .05$ ). That is,

males with higher fat stores have accelerated adrenal maturation. After controlling for age, DHEA-S is significantly correlated with BMI-R ( $r = 0.26$ ,  $P < .05$ ), but not adiposity ( $r = 0.16$ ,  $ns$ ). In order to look more closely at the non-significant relationship between DHEA-S and the adiposity measure among males, partial correlations (controlling for age) were performed for each of the skinfold measures that compose the adiposity measure (i.e. triceps, subscapular, and suprailliac). Results show that only the triceps skinfold is



**FIGURE 1** Age-related change in adrenal maturation (DHEA-S) for males and females. Values represent untransformed data in pg/min.



**FIGURE 2** Adrenal maturation by age for males and females with better and worse nutritional status. DHEA-S is shown in untransformed pg/ml.

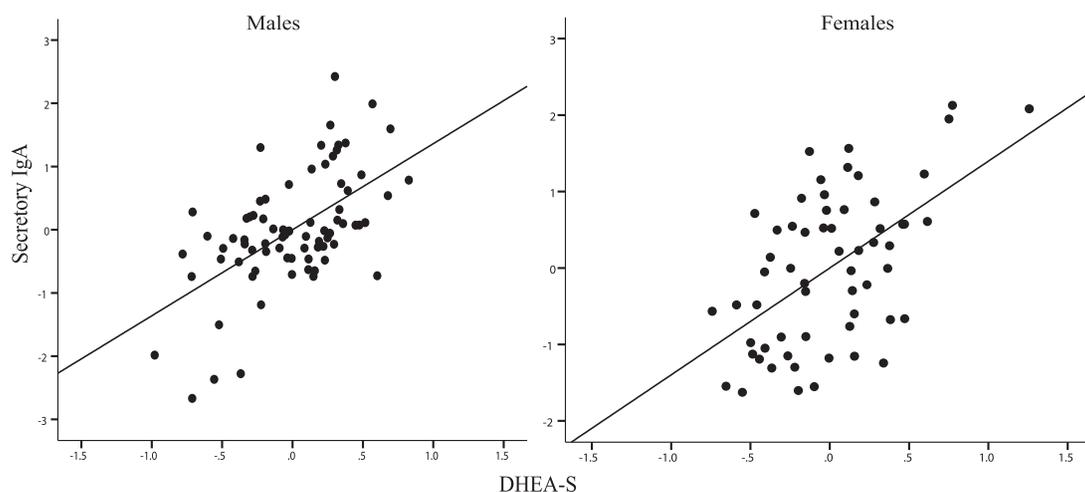
unrelated to DHEA-S ( $r = 0.14$ , *ns*). Suprailliac is significantly associated with DHEA-S ( $r = 0.33$ ,  $P < .01$ ) and subscapular approaches significance ( $r = 0.21$ ,  $P = .07$ ). DHEA-S was not associated with either measure of fat stores in females: adiposity ( $r = 0.11$ , *ns*), BMI-R ( $r = 0.05$ , *ns*). DHEA-S was also not associated with any of the skinfold measures for females ( $r = 0.16$ ,  $0.11$ ,  $0.08$ , *ns*, for triceps, subscapular and suprailliac, respectively). Figure 2 represents the relationship between DHEA-S and age for males and females with high and low nutritional status. The slope of the association is stronger for males with high BMI-R, suggesting that differences in DHEA-S between males high and low in BMI-R increase with age.

### 3.4 | What is the relationship between adrenal maturation and mucosal immunity?

DHEA-S and sIgA were strongly correlated for both males ( $r = 0.64$ ,  $P < .001$ ) and females ( $r = 0.55$ ,  $P < .001$ ; see

Figure 3). As a second step, we used multiple regression to predict DHEA-S levels separately for each sex while controlling for the effect of age and overall energy budget (ie BMI-R) in order to adjust for phenotypic correlations (Blackwell, Snodgrass, Madimenos, & Sugiyama, 2010). Using this model, DHEA-S is a strong, unique predictor of sIgA in both males ( $\beta = 0.67$ ,  $P < .001$ ) and females ( $\beta = 0.57$ ,  $P < .001$ ). Age and BMI-R contribute no additional variance to sIgA when DHEA-S is included in the model ( $R^2$  change =  $0.03$ , *ns*, for females and  $0.01$ , *ns*, for males). See Table 3, Model 1.

As a final step, a path analysis was conducted to assess potential causal pathways between BMI-R, age, DHEA-S, and sIgA. The model—presented in Figure 4 (males) and Supporting Information Figure S1 (females)—shows that BMI-R and age do not directly affect sIgA (ie the pathways from BMI-R [ $\beta = -0.11$ , *ns*] and age [ $\beta = 0.08$ , *ns*] are not significant), but do so indirectly via upregulation of DHEA-S ( $\beta = 0.71$ ,  $P < .001$ ). The results of the path analysis



**FIGURE 3** DHEA-S by sIgA (controlling for age and BMI-R) for males and females.

**TABLE 3** Multiple regression models predicting mucosal immunity, growth, and strength among Tsimane adolescents

	Males	Females	Males	Females	Males	Females
Model 1	Predicting sIgA					
Age	-0.04	-0.15	...	...	...	...
BMI-R	0.08	0.08	...	...	...	...
DHEA-S	0.67***	0.57***	...	...	...	...
Model 2 (A, B, C)	Predicting height					
Age	0.78***	0.74***	0.83***	0.77***	0.80***	0.78***
BMI-R	0.16**	0.20*	0.18**	0.23**	0.17**	0.22**
DHEA-S	0.12†	0.10	...	...	0.09	-0.04
sIgA	...	...	0.07	0.22**	0.03	0.25**
Model 3 (A, B, C)	Predicting strength					
Age	0.76***	0.82***	0.84***	0.82***	0.77***	0.84***
BMI-R	0.26***	0.32***	0.30***	0.34***	0.27***	0.34***
DHEA-S	0.16**	-0.02	...	...	0.19**	-0.09
sIgA	...	...	0.03	0.09†	-0.06	0.13*

Entries are standardized  $\beta$ -values.

Note. DHEA-S, dehydroepiandrosterone-sulfate secretion rate; sIgA, salivary IgA secretion rate. Variance inflation factors were normal ( $<5$ ) for predictors in all models.

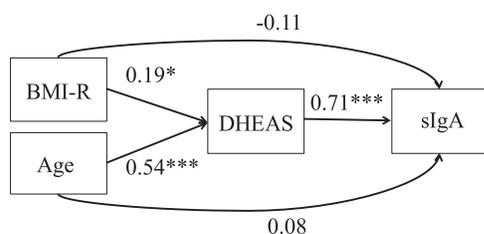
† $P = 0.10$ , \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

accord with the theoretical model presented earlier: greater energetic availability boosts adrenal development, which increases investment in mucosal immunity. In other words, the adrenal gland appears to mediate the relationship between energy availability and mucosal immunity. For females, BMI-R was not a direct predictor of DHEA-S ( $\beta = -0.11$ , *ns*), but age was ( $\beta = 0.27$ ,  $P < .05$ ). DHEA-S was a strong predictor of sIgA ( $\beta = 0.57$ ,  $P < .001$ ).

We also test an alternative model where BMI-R and age predict sIgA, which then predicts DHEA-S (i.e. sIgA and DHEA-S switch places in the path model; see Supporting Information Figures S2 and S3). In the initial model, depicted in Figure 4, the relationship between age and sIgA ( $r = 0.34$ ,  $P < .01$ ; see Tables 1 and 2) among males disappears when the pathway through DHEA-S is added (ie full mediation; Baron & Kenny, 1986), suggesting that the relationship between age and sIgA is an artifact of the pathway from age to DHEA-S and from DHEA-S to sIgA. In the alternative model, BMI-R ( $\beta = 0.16$ ,  $P < .05$ ) and age

( $\beta = 0.38$ ,  $P < .001$ ) significantly predict DHEA-S among males, even when sIgA (as a potential mediator) is controlled. Therefore, in addition to having less theoretical and empirical evidence to support it, the alternative model shows no evidence for mediation. For females, the conclusion is the same: age directly affects DHEA-S ( $\beta = 0.40$ ,  $P < .001$ ) even when sIgA is controlled (BMI-R predicts neither DHEA-S nor sIgA). See also Tables 1 and 2 for zero-order correlations.

Finally, we explore a second alternative model where BMI-R is an outcome of DHEA-S rather than an input (see Supporting Information Figures S4 and S5). Conceptually, age may upregulate DHEA-S as normal maturation occurs, which separately affects BMI-R and sIgA. This presents an attractive alternative for males, as age predicts DHEA-S ( $\beta = 0.56$ ,  $P < .001$ ) and DHEA-S predicts BMI-R ( $\beta = 0.31$ ,  $P < .05$ ). However, because age and BMI-R are not correlated ( $r = 0.04$ , *ns*), this model also lacks mediation. See supplement for standardized Beta values.



**FIGURE 4** Path analysis representing the predicted causal relationships among males. Entries are standardized  $\beta$  values.

### 3.5 | Does investment in adrenal maturation trade-off with investments in skeletal growth and/or strength?

A final goal was to assess possible trade-offs between adrenal maturation, mucosal immunity, and investment in growth—height and muscle mass (measured as strength). As a first step, we examine partial correlations, controlling for age. For males, DHEA-S and height show a significant positive

association ( $r = 0.27$ ,  $P < .05$ ). Further, in accordance with life-history theory, males with higher adiposity ( $r = 0.39$ ,  $P < .001$ ) and BMI-R ( $r = 0.36$ ,  $P < .001$ ) also have faster growth (i.e. greater height-for-age). For females, those with higher adiposity ( $r = 0.39$ ,  $P < .001$ )—but not BMI-R ( $r = 0.09$ , *ns*)—have greater growth. Mucosal immunity is not positively correlated with height ( $r = 0.15$ , *ns*) and strength ( $r = 0.08$ , *ns*) in males. Among females, mucosal immunity is positively associated with height ( $r = 0.29$ ,  $P < .05$ ) but not strength ( $r = 0.10$ , *ns*).

As a second step, multiple regressions was used to examine the relationship between adrenal investment, immunity, and growth separately for males and females. We include BMI-R in the model to adjust for phenotypic correlation, and age to draw out maturational relationships. For males, DHEA-S approaches significance as a positive predictor of height ( $\beta = 0.12$ ,  $P = .10$ ), controlling for age ( $\beta = 0.78$ ,  $P < .001$ ) and BMI-R ( $\beta = 0.16$ ,  $P < .01$ ). For females, only age ( $\beta = 0.74$ ,  $P < .001$ ) and BMI-R ( $\beta = 0.20$ ,  $P < .05$ ) were significant predictors of height. See Table 3, Model 2A.

Relationships with strength show similar results. For males, DHEA-S is a significant predictor of strength ( $\beta = 0.16$ ,  $P < .01$ ), controlling for age ( $\beta = 0.76$ ,  $P < .001$ ) and BMI-R ( $\beta = 0.26$ ,  $P < .001$ ). Again, for females, only age ( $\beta = 0.82$ ,  $P < .001$ ) and BMI-R ( $\beta = 0.32$ ,  $P < .001$ ) were associated with greater strength. See Table 3, Model 3A.

In separate models, we examine sIgA-growth associations (i.e. without DHEA-S), controlling for age and phenotypic correlation. sIgA is a significant positive predictor of height ( $\beta = 0.22$ ,  $P < .01$ ) in females but not males ( $\beta = 0.07$ , *ns*). Similarly, sIgA approaches significance as a predictor of strength in females but not males. Age and BMI-R were strong significant predictors of growth in both males and females. See Table 3, Models 2B and 3B for  $\beta$  values.

As a third step, we add DHEA-S to Models 2C and 3C to control for adrenal maturation in assessing the immunity-growth relationship. Among males, neither DHEA-S ( $\beta = 0.09$ , *ns*) nor sIgA ( $\beta = 0.03$ , *ns*) were significant predictors of height and only DHEA-S was a significant predictor of strength ( $\beta = 0.19$ ,  $P < .01$ ; sIgA:  $\beta = -0.06$ , *ns*). Among females, sIgA was a significant positive predictor of both height ( $\beta = 0.25$ ,  $P < .01$ ) and strength ( $\beta = 0.13$ ,  $P < .05$ ). As in other models, age and BMI-R were strong significant predictors for both sexes. See Table 3, Models 2C and 3C for  $\beta$  values.

## 4 | DISCUSSION

In this study, we apply a life-history framework to understand variation in adrenal maturation in a population of Bolivian juveniles and adolescents. Our results suggest that maturation of the adrenal gland, energetic status, mucosal

immunity, and physical growth are all highly intertwined in ways that are moderately sex-specific in this population.

### 4.1 | Is adrenal maturation subject to energetic constraints?

We examined the extent to which overall energy budget is associated with inter-individual variation in DHEA-S levels in males and females. Among males, DHEA-S was significantly associated with 2 proxies of energetic status after controlling for age; that is, males with higher BMI and body fat secrete more adrenal androgens. This result parallels the robust relationship between higher energy budget and earlier gonadarche in humans; adolescents in better nutritional condition have higher testosterone levels (Hodges-Simeon et al., 2015) and earlier menarche (Gurven & Walker, 2006; Lassek & Gaulin, 2007). Further, this suggests that adrenal maturation is costly and subject to constraints; that is, only those with sufficient postnatal energy reserves will invest in accelerated maturation (cf. Ong et al., 2004).

In prior research, the empirical relationship between measures of body fat and adrenal androgens shows conflicting results. One longitudinal study of adolescents found that increases in BMI were associated with increases in DHEA-S (Remer and Manz, 1999). Further, adrenarche begins around the time of the adiposity rebound (Smith et al., 1989), and adrenal androgens are elevated in obese children (Shalitin & Phillip, 2003). Several studies have found no relationship between DHEA or DHEA-S (DHEA/S) and measures of adiposity, while others indicate that DHEA/S concentrations may be inversely associated with body fat (for a review, see Tchernof & Labrie, 2004). DHEA supplementation has also been shown to result in decreased body fat (Nestler et al., 1988; Villareal & Holloszy, 2004). Most of these studies target adults or atypical (i.e. obese) adolescents; therefore, the relationship between DHEA/S and energy budget may depend on life history stage (i.e. adolescence vs. adulthood). Further, these studies were all conducted in energy-abundant wealthy nations, where adults are typically characterized by excess adiposity. In this study, we examine the relationship between energy availability and adrenal maturation in an energy-limited population with high parasite loads, the Tsimane, where lower body fat may make trade-offs between energy and adrenal maturation more critical.

Deficits in adrenal maturation may have important consequences for juvenile and adolescent development. Evidence suggests that DHEA and DHEA-S modulate immunological components (Daynes et al., 1990; Di Santo et al., 1996; Suzuki, Suzuki, Daynes, & Engleman, 1991), and are protective against infection incidence and severity in adolescence (Kurtis, Mtalib, Onyango, & Duffy, 2001; Leenstra et al., 2003). Adolescents and children with decreased adrenal

androgens may also be at risk for depression (Goodyer et al., 1996). Therefore, deficits in adrenal androgens, as a byproduct of life-history trade-offs, have important impacts on the developing individual's overall health.

Surprisingly, DHEA-S was unrelated to either BMI-R or adiposity in females after controlling for age. It is unclear why energy and DHEA-S maturation would be linked in males but not females in the present sample. Other studies find that DHEA-S is positively associated with BMI-for-age Z-scores in adolescent Kenyan females (Leenstra et al., 2003), and sum-of-skinfolds (which is similar to our adiposity measure) in females in the Philippines (Coutinho et al., 2007). Several reasons may explain this discrepancy. First, evidence suggests that DHEA-S has both sex- and site-specific effects on adipose tissue (Hernández-Morante, Pérez-de-Heredia, Luján, Zamora, & Garaulet, 2008), so sex differences may be dependent on methods of adipose measurement. Among males in the present sample, DHEA-S was associated with suprailliac skinfolds (and, marginally, subscapular skinfolds), but not triceps skinfolds. Second, male adrenal development may be more sensitive to energetic constraints than female development. Sexual dimorphism in height increases with improvements in living conditions (Kuh, Power, & Rogers, 1991; Tanner, 1982), suggesting that females may be more buffered from environmental stresses on growth than males (Stinson, 1985) or that males convert an energy advantage to height or strength whereas females do not.

#### 4.2 | What is the relationship between adrenal maturation and mucosal immunity?

The relationship between adrenal androgens during maturation and sIgA is not well studied. We find that DHEA-S and sIgA are strongly positively correlated in both males and females after controlling for both age and proxies of energy budget. These results suggest that, alongside other immunological agents, DHEA-S may act to bolster immunocompetence via increases in mucosal immunity, potentially independently of energy balance.

DHEA/S is often characterized as beneficial to health and immune function (Casson et al., 1993; Padgett, Sheridan, & Loria, 1995; for a review see Hazeldine, Arlt, & Lord, 2010; Kroboth et al., 2011), including (but not limited to) suppressing inflammatory cytokines (Di Santo et al., 1996), increasing IL-2 secretion (Daynes et al., 1990), and increasing T-cell activity (Suzuki et al., 1991). More relevant to the current paper, in several studies of adolescents in Kenya and the Philippines, DHEA-S was inversely associated with *Plasmodium falciparum* and *Shistosoma* parasitemia independent of age (Kurtis et al., 2001, 2006; Leenstra et al., 2003). These studies showed that those with higher investment in adrenal maturation showed better disease resistance;

however, this association may stem from DHEA's action on the parasite rather than the host immune system (Zhang et al., 2017). Conversely, DHEA/S has been negatively associated with some measures of immunity. For example, DHEA-S was negatively associated with complement protein activity in both humans and orangutans (Prall et al., 2015; Prall and Muehlenbein, 2015), and some evidence suggests that DHEA may inhibit lymphocyte proliferation under some circumstances (Sakakura, Nakagawa, & Ohzeki, 2006). These studies suggest that DHEA/S likely does not modulate all aspects of immunity in the same way and that the present results may not extend to other immunological measures.

Although this study was not designed to test whether DHEA-S exerts direct, mechanistic actions on the expression of sIgA in saliva, research on DHEA/S and other androgens in laboratory rodents suggests that such direct action is physiologically possible (Kaetzel, 2005). Indeed, while some view adrenal androgens as primarily precursor hormones (Labrie et al., 1998), results of this and other studies suggest that healthy adrenal androgen secretion is crucial to immunocompetence. Given that DHEA and DHEA-S appear to modulate immunological activity in diverse age and sex-specific ways, future research should consider ecological and evolutionary explanations of this androgen's modulation of specific aspects of immunocompetence, with considerations of the life-history strategy of the organism and the specific disease burden of the population.

Two aspects of the disease ecology of the Tsimane make this an interesting population with which to address these questions. First, respiratory infections are common among the Tsimane. Infant and child mortality is high; as of 2002, 15% of children born did not reach their fifth birthday (Gurven et al., 2007) and two-thirds of early childhood deaths were due to infectious disease, of which respiratory infections account for half (Gurven et al., 2007). Lower sIgA has been associated with an increased incidence of upper respiratory infections (Drummond & Hewson-Bower, 1997; McClelland, Alexander, & Marks, 1982). Second, the Tsimane experience an extremely high rate of dental caries, which are associated with higher sIgA (Thaweboon, Thaweboon, Nakornchai, & Jitmaitree, 2008). Thus, Tsimane children may upregulate sIgA as an adaptive response to higher levels of respiratory and cariogenic pathogens. The demand for mucosal immunity in this population may constitute a significant draw on energetic budgets.

#### 4.3 | Does investment in adrenal maturation or mucosal immunity trade-off with investments in skeletal growth and/or strength?

Trade-offs between life-history demands are unavoidably confounded by phenotypic correlation—the fact that those with

higher energy budgets are able to invest more in multiple life-history traits. Phenotypic correlation leads to positive correlations between these traits rather than the negative correlations expected from life-history trade-offs. In this study, we attempted to control for phenotypic correlation by including proxies of energy status in our models (Blackwell et al., 2010; McDade, Reyes-García, Tanner, Huanca, & Leonard, 2008). Despite this control, we found remaining positive associations between investment in adrenal maturation and growth in height and muscle mass, suggesting that those in better condition are able to allocate increased energy across multiple domains. Similarly, adrenal maturation may act as one of the conductors orchestrating development; the soma may invest in adrenarche when it can afford all the changes that maturation will trigger. These findings accord with studies showing that DHEA-S is associated with increased bone growth and height velocity (Remer et al., 2003; Zemel & Katz, 1986); however, these prior studies did not control for phenotypic correlation.

Life history theory also suggests that investment in immune function and growth will trade-off (McDade, 2003; Muehlenbein & Bribiescas, 2005); for example, those with a high pathogen load experience delays in growth (eg Blackwell et al., 2010). In this study, despite controlling for potential phenotypic correlation, mucosal immunity and growth (in height and strength) show positive associations (females only) rather than the expected negative relationship. Like the association between DHEA-S and growth, these results also suggest that those in better overall condition have greater investment across all costly biological demands. Either trade-offs do not exist (or are only present in very compromised individuals) or BMI-R is an inadequate measure of phenotypic correlation. Adding DHEA-S to this model did not draw out trade-offs between sIgA and growth.

#### 4.4 | Evolutionary origins of adrenal maturation in humans

The study of adrenal maturation within a life-history and evolutionary framework is complicated by an incomplete understanding of the origins of this physiological domain during human evolution. Phylogenetically, human adrenarche may derive from the slowing of human life histories, suggested by the finding that in macaques, adrenarche occurs in the first few months of life (Conley et al., 2011), while apes experience adrenarche much later (Behringer, Hohmann, Stevens, Weltring, & Deschner, 2012). However, it is still unclear what type of ultimate, functional role adrenarche plays in human life history. Recent attention to this question (Campbell, 2011; Del Giudice, 2009) has brought this developmental phase into the spotlight, but much is still unknown. The adrenarchal rise in DHEA/S levels in humans coincides with the transition from childhood to juvenility (Bogin, 1999),

recently termed the juvenile transition. Based on some of the physiological activity of DHEA/S, as well as the timing of increased synthesis, Campbell (2006, 2011) argues that DHEA/S plays an important role in the developing brain via shifts in energy allocation and glucose utilization, among other effects, in supporting extended brain maturation and cognitive development. Therefore, adrenarche may be viewed as initiating an allocation shift to investment in cognitive maturation, important to the unique life-history strategies of apes. A related approach views adrenarche as a mechanism to support important cognitive and social development during the juvenile transition. Del Giudice (2009) argues that adrenarche and the production of adrenal androgens act to organize endocrine pathways in tandem with biosocial factors that influence an individual's assay of social situations, calibrating the individual's life-history strategy accordingly. Under this view, the timing and production of adrenal androgens act as the mechanism to orchestrate development via physiological modulation of reproductive endocrinology.

Although these authors propose promising ideas about the adaptive role of adrenal androgens during the juvenile period, a full description of how the features of this stage solve the particular adaptive problems emerging at that stage of development remains inchoate. In this paper, we focus on the role of DHEA/S in immunity and growth during late juvenility and adolescence, and offer evidence suggesting that DHEA/S plays a central role in promoting immunity. Adrenal maturation begins at approximately 6 to 8 years of age, reaching its peak in early adulthood. What role might increase investment in immunocompetence play during this phase of life? Juvenility is characterized by increased feeding and locomotor independence, and a significant broadening of the social sphere including affiliative and competitive relationships (Bogin, 1999). Greater investment in immunity may be required to offset elevated pathogenic exposure that results from a widening of the physical and social space that the juvenile increasingly inhabits. Therefore, the demands of cognition and immunity in juvenility may both stem from the same underlying selection pressure: elevated levels of social interaction. For males, entrance into the wider social world necessarily involves the passage into status competition, dependent upon both size-based and cognitive resources. Recent research suggests that it is DHEA—and not cortisol or testosterone—that increases in response to physical competition among human juvenile males (McHale, Zava, Hales, & Gray, 2015). Regulation of DHEA/S in response to energetic availability may play a role in mediating low-stakes competition for males during this period (Bogin, 1999). Further, for females, commencement of sexual activity poses immunological challenges for the mucosa of the genital tract. Future research should investigate the extent to which adrenarche orchestrates development in sex-specific ways.

## 4.5 | Limitations and future directions

Despite a large sample size from a population of anthropological interest living under natural conditions, there are a number of limitations that restrain interpretation of the present results. Although multiple saliva samples from a single individual may have yielded more approximate baseline hormone levels, only single samples were used here. However, DHEA-S is thought to be more stable than many other salivary androgens, and there is no current literature guiding sampling requirements and limitations. Additionally, the cross-sectional design of the study limits our ability to make causal inferences; longitudinal sampling of hormones associated with growth and change in immunity is an important target for future research. DHEA-S, as well as DHEA, is under control of the HPA axis, and thus chronic stress is associated with reductions in DHEA-S, while acute stress elevates DHEA-S concentrations (Lennartsson, Kushnir, Bergquist, & Jonsdottir, 2012; Lennartsson, Theorell, Rockwood, Kushnir, & Jonsdottir, 2013). Although it is unlikely in this context, variability in psychological stress in this sample may have caused some variability in adrenal androgen results. Third, while DHEA and DHEA-S are often highly correlated (eg Prall et al., 2015), we only measured DHEA-S as part of this study, and cannot determine whether these findings are related to the effects of DHEA or DHEA-S, or some other down-stream metabolite. Finally, sIgA is only a single immunological marker. Although it was chosen here for ease of measurement, future studies should use multiple measures of innate, cell-mediated, and humoral immunity to better understand how androgens shape different immunological processes during development.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

## AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the article.

*Analyzed the data and drafted the article:* Hodges-Simeon, Prall

*Designed the study and directed implementation:* Hodges-Simeon

*Data collection:* Hodges-Simeon

*Logistical support:* Gurven, Gaulin

*Edited the article for intellectual content and provided critical comments on the article:* Hodges-Simeon, Gurven, Gaulin, Prall, Blackwell

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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