THE TIMING OF ADRENARCHE IN MAYA GIRLS, MERIDA, MEXICO

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ABSTRACT (214 words but can be up to 350)

In this pilot study we investigated age at adrenarche and body composition among 25 urban Maya girls aged 7-9 living in low-income, urban households in Merida, Mexico. Adrenarche involves the maturation of the hypothalamic-pituitary-adrenal axis and increased production of the adrenal androgens dehydroepiandosterone (DHEA) and its sulfate ester (DHEA-S). It occurs around age 6-8 in contemporary, industrialised populations among whom adrenarche has been studied from a primarily clinical perspective and, developmentally, marks the transition from childhood to juvenility. The few available studies of adrenarche in subsistence level populations, however, indicate a later age (8-9) than suggested by industrialized groups. It is linked to the appearance of some secondary sexual characteristics and some studies associated it with body composition, particularly, the timing of the BMI (what others term adiposity) rebound. Since the urban Maya in Merida are undergoing a nutritional transition and increases in overweight/obesity, we hypothesized that adrenarche -- assessed using salivary levels of DHEA-S -- would occur earlier among Maya girls. The hypothesis was rejected since adrenarche occurred later than expected at close to 9 years. Nevertheless, overweight or obese girls were more likely to have undergone adrenarche, whereas pre-adrenarcheal girls were smaller and thinner. Further studies and larger sample sizes are required to illuminate how adrenarcheal variation relates to body composition, pubertal progression and developmental plasticity in other non-Western populations.

INTRODUCTION

The human life cycle includes an extended period of childhood and juvenility characterised by relatively slow growth, followed by a distinctive adolescent growth spurt and delayed sexual maturation relative to our closest primate relatives (Bogin 1997; Stulp and Barrett 2014; Muehlenbein and Flinn 2011; Houghton 2013; Cameron and Bogin 2013). The transition from childhood to the juvenile period (Bogin 1999) or what is commonly called *middle childhood* by developmental psychologists -- is marked by the milestone of adrenarche. It is a biochemical and hormonal threshold in the maturation of the hypothalamic-pituitary-adrenal (HPA) axis, along with the development of the *zona reticularis* layer of the adrenal gland. This causes the re-initiation of adrenal androgen production, namely, dehyroepiandosterone (DHEA) and its more stable form dehyroepiandosterone sulphate (DHEA-S) (Belgorosky et al., 2008; Havelock et al., 2004; Maninger et al., 2009).

In humans, DHEA and DHEA-S are the most abundant steroid hormones in circulation (Maninger et al. 2009; Ogino et al., 2016), although other mammals produce high levels in the brain. Levels of these hormones are high in humans during perinatal development, decline rapidly in the first months postnatally, until increasing again from adrenarche until age 20-30, after which they gradually decline (Greaves et al., 2019; Quinn, Robinson, & Walker, 2018).

Among industrialised, well-nourished populations, the observed mean age of adrenarche ranges from 6-8 years (Maninger et al. 2009; Havelock, Auchus, and Rainey 2004), and the clinical threshold of DHEA-S considered to mark the adrenarcheal transition is >40-50µg/ml in plasma (Grumbach, 1980), or 400 pg/ml in saliva (Houghton, Cooper, Booth, et al. 2014). However, the range of variation in age at adrenarche and associated DHEA-S levels has not been well studied in populations exposed to more challenging ecological conditions during development. Clearly, however, the timing of adrenarche plays an important role in demarcating early life history stages in humans (Bogin, Varea, et al. 2018; Campbell 2006; Hochberg, 2008). Variation in timing of this developmental transition may shed light on the extent of phenotypic plasticity typical of humans during their long childhood.

Functionally, adrenarche plays an important role in social and neurological development at the transition between childhood and juvenility when children demonstrate greater independence and cognitive abilities (Campbell 2006; Gogtay et al., 2004; Greaves et al., 2019). For example, Campbell (2006) has suggested that, given the neurological functions of DHEA-S, rising levels of this hormone during the adrenarcheal transition are crucial for cortical maturation and synaptic modification that translates phenotypically into the documented increase in childhood capabilities. Del Guidice (2014) also argues that adrenarche functions as a critical switch point in life history development that, in co-ordinating life experiences up to that point, can determine an individual's later biological fitness. Although an extended period of childhood growth is unique to humans, adrenarche occurs among a range of primates at different ages depending on the life history of the species (Bernstein et al., 2012; Sabbi et al., 2019). For example, the increase in DHEA-S associated with adrenarche is more subdued in gorillas and occurs earlier than in either humans or chimpanzees. Similarly, gorillas grow faster and reach sexual maturation earlier than members of either *Homo* or *Pan* (Bernstein 2016).

It remains unclear how the adrenarcheal onset is mediated, and if there is a specific physiological trigger. In humans, adrenarche coincides with the BMI (body mass index) rebound in childhood, and is closely tied to acceleration of somatic development (Rolland-Cachera et al. 2006; Houghton 2013; Remer 2000; Campbell 2006). However, the role of body composition of muscle or adipose tissue in relation to adrenarcheal onset is controversial (Bogin, 2020), and some studies have found no association between BMI and adrenarche (e.g., Mouritsen et al., 2013). In contrast, Remer (2000), using a longitudinal design of children, showed that periods of increased BMI were associated with higher DHEAS levels. The BMI, however, is an imperfect measure of variability in adiposity, as excess weight for height can also be caused by increased muscle mass, body water, or shorter leg length independent of differences in adiposity (Freedman et al. 2005). In a different project undertaken with pre-pubertal children, both obesity and elevated leptin levels correlated with higher adrenal androgen levels (Genazzani, Pintor, and et al. 1978) pointing to some role of nutritional status and rising levels of adrenal androgens. It is also possible that the growth axis, through the effects of growth hormone, insulin-like growth factor and insulin, is involved in the modulation of adrenal androgen production (Belgorosky et al. 2008). Finally, in industrialized, affluent settings it was found that psychological stress and early life familial adversity might accelerate adrenarcheal development (Belsky et al. 2003), whereas high quality parental investment and less familial conflict were found to delay adrenarcheal onset until a later age (Ellis and Essex 2007). Houghton et al. (2019) have also suggested that stress caused by having a mother diagnosed with breast cancer could accelerate adrenarcheal development.

From an evolutionary perspective, life history theory posits that organisms have evolved the capacity to respond to local environmental conditions by adjusting their developmental trajectories accordingly (Wells et al. 2017; Ackermann and Pletcher 2010; Worthman 1999; Mcintyre and Kacerosky 2011). One mechanism through which organisms shape later life traits to early environmental cues is through developmental plasticity during critical periods in early life (Bogin 1999; Lea et al. 2017; Bogin, Varela-Silva, and Rios 2007; Kaplan, 1954; Lasker, 1969). Del Giudice et al. (2009) have argued that adrenarche is part of a developmental switch point following an extended childhood period during which environmental and genetic factors are integrated to adjust and adapt an individual's life history. In their studies of how early life development in different ecological settings affects adult levels of reproductive steroids in Bangladeshi migrants to the UK, Núñez de la Mora et al. (2007) and Magid et al. (2018) have also suggested the existence of a critical developmental transition around age 8 in both girls and boys, after which the effects of specific ecological conditions have limited ability to adjust physiological settings that influence later life adult reproductive function.

Adrenarche is associated with the appearance of some secondary sexual characteristics, such as axillary hair, an increase in sebaceous gland secretion, acne, and changing body odour (Leung and Robson 2008; Idkowiak et al. 2011; Ibáñez et al. 2000). In this context, it has been primarily studied by clinicians in children diagnosed with premature development of pubic hair or pubarche (usually one of the later phenotypic changes accompanying puberty), who were often also born small for gestational age (SGA). Premature pubarche together with relatively high levels of adrenal androgens has prompted a definition of "precocious" or "premature adrenarche" (Ibáñez et al., 2000; Leung and Robson, 2008; Novello and Speiser, 2018). Some clinicians even equate the two phenomena (pubarche and adrenarche) even though these are normally temporally separate (e.g., Novello and Speiser, 2018). SGA infants who experience rapid catch-up growth appear to be at particular risk for premature adrenarche (Ibáñez et al., 2000). A study of Turkish girls with this condition found that they had higher height- and weight-for-age standard deviations compared to a control group, and also had higher body fat percentages but lower fat free mass, body water, and muscle mass compared to their pre-adrenarcheal peers (Cebeci and Taş 2015). Girls with precocious adrenarche are also known to be at risk for increased waist circumference (WC) in adulthood, polycystic ovarian syndrome and metabolic syndrome (Ibáñez, Potau, and Carrascosa 1998; Dimartino-Nardi 1998; Banerjee et al. 1998; Efthymiadou et al. 2019), all health conditions with lifelong consequences. However, these health issues may be related more to being SGA than experiencing an earlier adrenarche per se (Hong and Chung, 2018; Mericq et al., 2017).

It is uncertain how the increase in DHEA-S during the adrenarcheal process is functionally (as opposed to temporally) related to the onset of puberty and maturation of the hypothalamic-pituitary-gonadal (HPG) axis (Clarkson and Herbison 2006). Most studies have suggested that the two processes are separate (e.g. Palmert et al., 2001 Sklar et al., 1980). More recently, however, research on androgen insensitive XY-patients indicated that androgens play an important role in determining the pattern of the timing of HPG-axis maturation (Papadimitriou et al., 2006). Two studies within the last decade have also found that girls with higher levels of adrenal androgens began the processes of gonadarche earlier than peers with lower levels (Houghton *et al.* 2019; Remer et al., 2010).

The steroid DHEA-S also binds to androgen receptors and functions as the precursor of testosterone and estradiol in peripheral tissues (Allison and Hyde 2013), where it is thought to be involved in the development of axillary and pubic hair, body odour, oily skin and acne (Leung & Robson, 2008). Furthermore, in the hypothalamus, where DHEA and DHEA-S act as neurosteroids, they can modulate $GABA_A$-receptors on the hypothalamic neurons that secrete gonadotropin-releasing hormone (GnRH) and corticotrophin-releasing hormone (CRH) (Sullivan and Moenter 2003; Gunn et al. 2015; Miklós and Kovács 2002). These neurons orchestrate the endocrine axes involved in reproduction (HPG) and stress (HPA), respectively, suggesting that DHEA-S might indeed play an important role in the maturation of these hormonal axes (Brunton 2015; Watanabe et al. 2014), and the management of different life history programmes (Wang, Luan, and Medzhitov 2019).

While studies of variation in adrenarcheal age among children have mostly derived from the clinical literature concerning precocious adrenarche among populations in industrialised countries, we know little about normal variation in adrenarche across different human groups exposed to various ecological settings during development. There is currently only one study of adrenarche from subsistence level populations. Helfrecht et al. (2017) compared DHEA-S levels obtained from hair samples collected from 480 children aged 3-18 in three sub-Saharan groups who varied in subsistence mode and ecology. These were: 1) Aka foragers living in the tropical rainforest of the Central African Republic (CAR); 2) Ngandu slash-and-burn horticulturalists who live in a symbiotic relationship with the Aka in the same CAR region; and 3) Sidama agropastoralists living in lowland southwestern Ethiopia and situated in a peri-urban environment. Helfrecht et al. (2017) estimated age at adrenarche as 9 years for the Aka and Ngandu, and 8 for Sidama children, both later than reports for industrialized populations. However, the atypical measurement of DHEA-S in hair samples limits the extent to which these results can be compared with others.

In a migrant project comparing 419 Bangladeshi and English girls who grew up in different environments, Houghton, Cooper, Booth, et al. (2014) used salivary samples of DHEA-S to explore ages at adrenarche. The Bangladeshi girls in this study were either living in Bangladesh or as first- and second-generation migrants in London, UK. The girls in Bangladesh came from the relatively affluent, middle-class, representing groups who have a history of migration to the UK. Although there has been upward mobility in younger generations of UK born-Bangladeshis, overseas-born Bangladeshis are among the most socioeconomically disadvantaged groups in the UK who tend to live in relatively deprived neighbourhoods (ONS 2011a, 2011b). The Bangladeshi migrants in London were compared to a group of British girls of European origin who attended either the same or nearby schools as the migrants. The median age at adrenarche (when girls passed the clinical threshold of DHEA-S levels) was similar for all groups except for the first-generation migrants: 7.2 years for girls still living in Bangladesh, 7.4 for second-generation girls in the UK, 7.1 for the girls of European origin and 5.3 years for the first-generation migrants (Houghton, Cooper, Booth, et al. 2014). The authors of this study suggested that rapid catch-up growth and an earlier BMI rebound might explain the significantly earlier age at adrenarche among the first-generation Bangladeshi migrant girls.

In the pilot study presented here, we investigated the adrenarcheal transition using salivary DHEA-S levels collected from a sample of 25 girls of Maya origin aged 7-9, living in the city of Merida, the state capital of Yucatan, Mexico. In the past 30 or so years, Merida has witnessed large-scale, rural-to-urban migration by Maya families in search of employment, together with rapid urbanization of southern parts of the city (Azcorra, Wilson, et al. 2013; Azcorra et al. 2015; ENSANUT 2012) (Azcorra et al. 2013, 2015; Dickinson et al., 1999; Instituto Nacional de Salud Pública, 2013). The Maya population now represents approximately one-third of the city's inhabitants and are among the most socioeconomically disadvantaged inhabitants. However, the majority of the population under study here lived in houses with concrete floors, had access to piped water and electricity, and their children regularly attended school (Wilson, 2011). The most striking characteristic is the evident nutritional transition, where traditional diets are being replaced by foods that are heavy in sugar (particularly sweetened drinks) and fats (fried foods) and a dearth of fruits and vegetables (Bogin et al. 2014; Wilson 2011; Bogin et al. 2020). Reports indicate that this population experiences a dual burden of malnutrition, with up to one third of children reported to be overweight and one fifth stunted (Azcorra, Varela-Silva, et al. 2013a, 2013b; ENSANUT 2012; Varela-Silva et al. 2009, 2012). At a regional level, the prevalence of stunting, documented in 2012 among children under 5 years in the southern region that includes Yucatan, was 15.8%, while overweight and obesity among school-aged children (5-11 years) was 19% and 12.5%, respectively (ENSANUT 2012). Given this scenario and the link between the timing of the BMI rebound and adrenarche, we hypothesised that age at this transition would be earlier among the Maya girls compared to adrenarcheal ages reported from Western groups.

MATERIALS AND METHODS

Participant recruitment

A subsample of 25 Maya girls who were part of a larger study of 58 children (31 boys and 27 girls) participated in the project here. The overarching aims of the larger study were to explore the effects of the dual burden of malnutrition on childhood growth and development (Wilson 2011; Wilson et al. 2011; Wilson et al. 2012). The larger sample included any Maya child aged 7-9 who was attending a state school and living at home with their biological mother in the southern part of Merida. The actual birth date of each child was known since most of the children were born in a local state hospital where they were issued a birth certificate. The girls' mothers were also included in the study; both child and mother had to have two (paternal and maternal) Maya surnames to be eligible to participate. Due to continued acculturation, only 13% of households spoke any Mayan and it was the primary language in only three households overall (Wilson 2011:83). Data for the present study were collected between February-August 2010.

Anthropometrics

Anthropometric data were obtained from all participants by five trained field workers using techniques described by Lohman et al. (1988). Measurements comprised height, weight, WC, mid-upper arm circumference, and a series of skinfolds (triceps, subscapular and suprailiac) measured in triplicate on the left side of the body. Body composition data were also obtained using bioelectric impedance. Participants were measured using a portable Martin anthropometer, a Seca portable scale (Model 881) calibrated before each measurement, a Harpenden calliper and Seca fiberglass tape measure. All participants were measured while wearing thin cloth shorts and shirts provided by the research team. Feedback on the children's data was provided to the mothers. The BMI was calculated using the standard formula (weight(kg)/height(m^2). Z-scores for height and weight were derived using Frisancho's Comprehensive Reference from NHANES III data as an appropriate standard for comparison of age-adjusted growth variables for the Maya (Frisancho 2008; Wilson 2011; Varela-Silva et al. 2009) .

Adiposity indicators

The BMI is an imperfect measurement to fully understand the effects of being overfat since alone it cannot discriminate the components contributing to excess weight (Freedman et al. 2005; Xiao et al. 2018). We therefore also assessed indicators of adiposity in relation to adrenarche (body fat percentage, fat mass index and fat free mass) using bioelectrical impedance. Measurements were taken in the field using a Maltron BioScan 916 (Maltron International Ltd). Participants lay on a mat without shoes, socks or any metal jewellery, with legs apart and arms away from their torsos and with measurements taken on the right side of the body using electrodes attached to the hands and feet. For precision readings, ideally, participants' liquid intake and physical activity should be monitored for 12 hours prior to measurement, but this was not feasible in the field. Using equations developed with 156 eleven-year-old children of Native American ethnicity in the USA (Lohman et al. 1999), body fat percentage was calculated (Wilson 2011; Wilson et al. 2012) using the following formula which makes use of skinfold thickness and bioelectrical impedance measurements (Lohman et al. 1999):

Eq. 1 Percentage body fat = 0.51 + 0.49*age (years) + 0.44*weight (kg) + 1.55*triceps skinfold thickness (mm) + 0.15*subscapular skinfold thickness (mm) + 0.54*(height (cm) ^{2}/resistance (Ω)) + 0.13*reactance (Ω)-0.04*triceps skinfold thickness (mm) * height (cm) ^{2}/resistance (Ω)) – 10.91

Fat mass and fat free mass (kg) were calculated using formulas validated by Ramírez *et al.* (2012) based on the deuterium oxide dilution technique, where the sample included 336 Mexican children aged 6-14 years including Maya girls;

Eq. 2: Fat free-mass (kg) = 0.661*stature (cm)^2/resistance (Ω) + 0.200*weight(kg) - 0.320

Children's fat mass was consequently calculated using the following equation:

Eq. 3: Fat mass (kg) = weight (kg) – fat-free mass (kg)

Fat mass index and fat free mass index respectively were consequently calculated using the formula:

Eq. 4a: Fat mass index = Fat mass/height (m) ^{2}

Eq. 4b: Fat free mass index = Fat free mass/height (m) ^{2}

The technical error of measurement for bioelectrical impedance was not calculated.

Birth weights were obtained from each child's health card issued to the mother at birth at the local clinic/hospital, which most mothers were able to produce at home. We used the WHO cut-off of <2.5 kg for determining low birth weight.

Pubertal Development Scale

Since some of the older children might have already entered the pubertal transition, mothers were given the Pubertal Development Scale (PDS) (~~Brooks-Gunn 1987;~~ Petersen et al. 1988) to complete for their daughters. The PDS has been extensively validated in different cultural settings (Chan et al., 2010; Houghton, Cooper, Bentley et al., 2014; Pompéia et al., 2019). Our modified version included questions concerning patterns of growth, development of breasts, body hair, body odour, and skin conditions (e.g., acne), since some of the variables relate to adrenarche and are useful for supplementing the hormonal data.

Saliva samples

A single saliva sample for later measurement of DHEA-S levels, was collected from each girl in the morning between 08:00 and 12:30 using passive drool, ensuring that at least one hour had passed after eating or drinking. It was not always possible to collect a saliva sample at the same time as the anthropometric data, but 54% (n=14) was either collected simultaneously or within one week, 19% (n=5) was collected within two weeks, 12% (n=3) within one month, 12% (n=3) within two months and only one sample (3%) within ten weeks of the anthropometry. Saliva samples were collected in 5 ml polypropylene vials using 2-3 pieces of a flavorless gum base (Cafosa©, Barcelona, Spain) as a stimulant. Samples were kept on ice and in portable freezers in the field until transported to the Aquatic Ecotoxicology Laboratory at Cinvestav-Merida, where they were kept at –80^{o}C until assayed.

Samples were analysed by ANM using a commercially available salivary DHEA-S enzyme-linked immunosorbent assay (ELISA) purchased from Salimetrics® (State College, CA). Samples were processed in a single batch according to manufacturer instructions and the absorbance of the ELISA plate was read using a Biorad microtiter plate reader at 450 nm without correction. The reproducibility of the assays was assessed by two pooled, blinded quality control samples in a single batch. The intra-assay coefficient of variation was 19.7%. The lower and upper limits of detection were 43 pg/ml and 16,000 pg/ml, respectively, whereas the lower limit of the functional range of the assay was 188.9 pg/ml. Any data point below assay sensitivity, but higher than the analytical sensitivity (43 pg/ml), was coded as being equal to the lowest standard (188.9 pg/ml). Since the clinical cut-off for adrenarche of 400 pg/ml in saliva was within the assay range of the DHEA-S kits, we classified any girl with a DHEA-S level below this range as pre-adrenarcheal.

Data Analyses

Absolute weight (kg), height (cm), BMI (kg/m^2), body fat percentage, fat mass index, and fat free mass index were analysed in association with adrenarcheal status using a non-parametric Mann-Whitney U test. Age- and sex-specific z-scores for body composition characteristics for weight, height, and BMI were derived and coded as binary variables, where girls above the sample median of z-scores for weight, height, and BMI-for-age were scored as 1, whereas girls equivalent or below the sample median were coded as 0. A Fisher's exact test was used to analyse the association between being above the adrenarcheal cut-off of 400 pg/ml ('post-adrenarcheal') and above the sample median z-scores for body composition variables.

We also tested for associations between the estimated adrenarcheal status of children (pre- or post-) and the 5^{th} percentile of z-scores for height-for-age (which marks the cut-off for stunting), the 5^{th} percentile weight-for-age (underweight), as well as the 5^{th}, 85^{th}, 95^{th} percentile of weight-for-age (wasting, overweight, and obesity respectively) (CDC 2013). Similarly, using a Fisher's exact test, we used the absolute fat percentage, fat mass index and fat free mas index to assess whether being above the sample median for these variables was associated with being post-adrenarcheal. Overfat was defined as being $>85^{th}$ sex- and age-specific reference curves for body fat derived from British children, as no equivalent exists for Maya children (McCarthy et al. 2006). Finally, we assessed birth weight and its association with adrenarcheal status using the sample median as well as the WHO definition of low birth weight (≤ 2.5 kg) (WHO 2014).

Statistical analyses were performed using Excel Version 16.29.1 and SPSS version 24. Significance levels were set at $p<0.05$.

Ethics

Girls who expressed interest in participating in the study were initially recruited through six local primary schools where meetings were held at the beginning of the school day to inform mothers about the project. Those who expressed interest were given information sheets and consent forms. Since not all mothers were literate, the study was also verbally explained before consent. In some cases, father signed the consent forms. Verbal assent was also obtained from the children prior to recruitment. Ethical approval was obtained from the Durham University Department of Anthropology Ethics Committee, and Loughborough University (R09-P145), the Comite de Bioetica para el Estudio con Seres Humanos in Mexico, and the Bioethics Committee of Human Studies of Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (Cinvestav). Approval for the project was also obtained from the Yucatan Minister of Education prior to any data collection. All data were stored in compliance with the UK Data Protection Act 1998, and later the General Data Protection Regulation 2018.

RESULTS

Table 1 presents descriptive statistics for the 25 girls participating in the present study. Mean age was 8.54 $\pm$ 0.68 years. Compared to NHANES III, the median height z-score (-1.01±0.90) of the study sample was more than one standard deviation below the median of the reference population. Using the ≤5th percentile cut-off, 40% of the participating girls could be classified as stunted. In contrast, only one girl was beneath the 5th percentile in weight-for-age, and the median weight z-score (-0.37±0.95) was only slightly below the reference median. On the other hand, 36% of the girls were overweight using the ≥85th percentile for BMI-for-age and 28% of the study sample was obese using the ≥95th percentile cut-off. The median BMI z-score of the girls in this study (0.50±1.06) was also slightly over the reference median. Using body fat percentage adjusted for age, 52% of the girls were overfat. Fat and fat free mass was significantly associated with being above the sample median for height z-scores (U=41.00, p=0.046 and U=23.00, p=0.002) and BMI z-scores (U=6.00, p<0.0001 and U=7.00, p<0.0001), but not weight z-scores (U=76.00, p=0.979 and U=71.50, p=0.767). Using the WHO cut-off of ≤2.5 kg, only three girls were born with low birth weight, and the sample median birth weight was 3.15±0.54 kg.

Adrenarcheal Status

Using the clinical cut-off point of 400 pg/ml for salivary DHEA-S, 6 girls were above this level and 19 were below (Fig.1). Fifteen (60%) of the 25 saliva samples fell below the functional sensitivity of the DHEA-S assay (<188.9 pg/ml). The mean age of the post-adrenarcheal girls in the sample was 9.0 ± 0.86 (SD) whereas the mean age of the pre-adrenarcheal girls was 8.3±0.56 (SD).

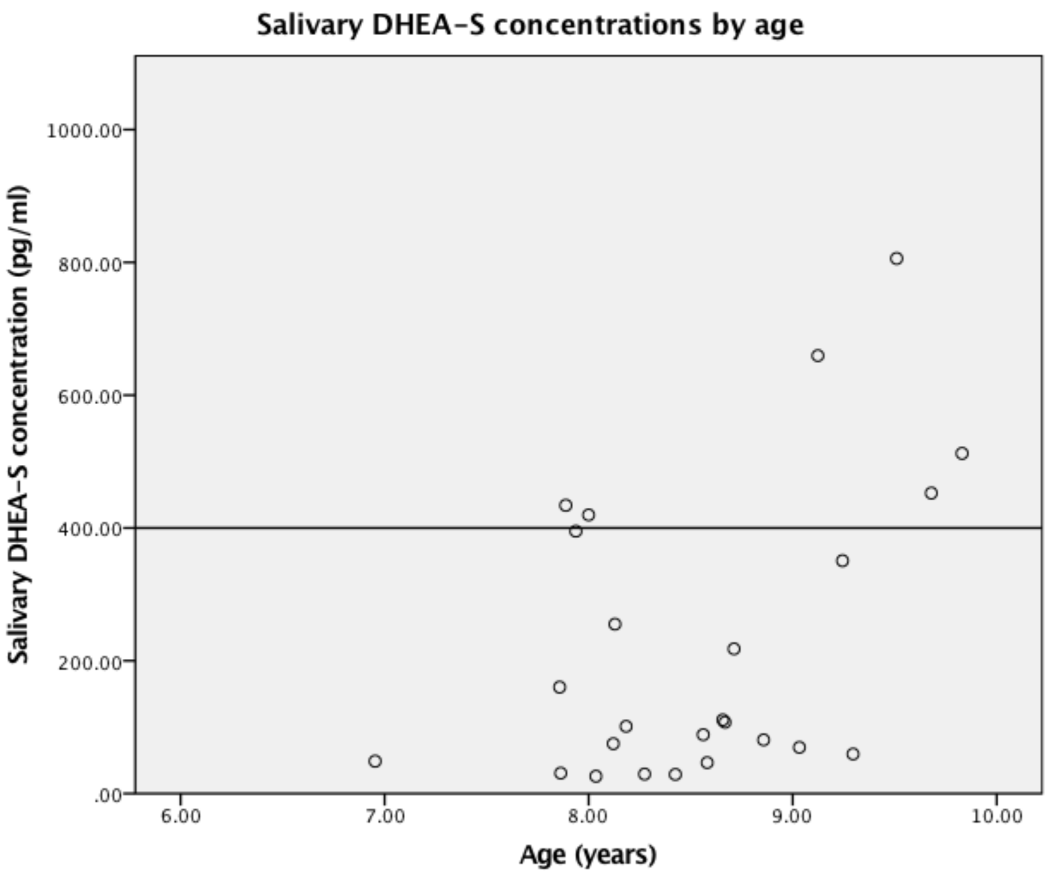


Figure 1: Salivary DHEA-S levels (pg/ml) and age (years) of 25 Maya girls from Merida, Mexico. The 400.0 pg/ml line indicates the salivary cut-off used to determine adrenarcheal status in Western clinical settings

ID	Age (years)	DHEAS levels (pg/ml)	Birth weight (kg)	Height (cm)	Height z-score	Weight (kg)	Weight z-score	BMI (kg/m^2)	BMI z-score	Body fat %	Fat Mass (kg)	Fat Free Mass (kg)	Fat mass index	Fat free mass index
1	9.3	59.49	2.75	124.7	-1.66	24.85	-1.09	15.98	-0.31	28.66	8.11	16.74	10.8	5.2
2	8.12	75.08	2.2	114	-1.95	20.8	-0.98	16	0.05	23.36	6.06	14.74	11.3	4.7
3	8.71	217.9	3.3	124.8	-1.19	32.45	0.26	20.83	1.37	34.58	9.12	23.33	15.0	5.9
4	8.67	107.3	3.2	124.7	-0.71	27.35	-0.14	17.59	0.54	30.42	5.91	21.44	13.8	3.8
5	8.58	46.5	2.93	124.4	-0.75	34.2	0.77	22.1	1.84	39.89	11.42	22.78	14.7	7.4
6	6.95	48.72	2.25	103.2	-2.89	17.6	-1.03	16.53	0.5	26.6	5.16	12.44	11.7	4.8
7	8.56	88.72	2.9	122.7	-1.01	34.8	0.84	23.11	2.07	37.18	14.86	19.94	13.2	9.9
8	9.03	69.51	3.75	128.7	-0.61	33.25	0.36	20.07	1.17	29.11	11.78	21.47	13.0	7.1
9	9.83	512.3	3.4	138.9	-0.12	36.5	0.22	18.92	0.57	32.9	11.78	24.72	12.8	6.1
10	9.68	452.5	N. A,	134.5	-0.24	43.25	1.16	23.91	1.94	46.84	18.67	24.58	13.6	10.3
11	7.94	395.1	3.5	123.6	-0.41	31.25	0.7	20.46	1.56	35.14	8.49	22.76	14.9	5.6
12	9.12	659.5	3.5	118.5	-2.15	39.05	1.01	27.81	2.79	42.47	16.99	22.06	15.7	12.1
13	8.13	255.1	2.8	113.1	-2.1	19.2	-1.32	15.01	-0.38	20.01	5.34	13.86	10.8	4.2
14	9.24	350.7	3.1	126.3	-1.43	27.75	-0.63	17.4	0.22	30.97	6.45	21.30	13.4	4.0
15	8.42	28.79	3.5	126.9	-0.38	34.5	0.8	21.42	1.67	34.56	13.03	21.47	13.3	8.1
16	9.51	805.9	3.75	133.3	-0.41	46.65	1.46	26.25	2.38	42.2	16.89	29.76	16.7	9.5
17	8	419.7	3.25	120.6	-0.88	22.05	-0.74	15.16	-0.31	25.97	3.57	18.48	12.7	2.5
18	7.86	30.67	3.5	113.6	-2.02	22.1	-0.73	17.13	0.5	26.71	5.23	16.87	13.1	4.1
19	8.27	29.31	2.7	118.3	-1.7	18.75	-1.71	13.4	-1.29	18.65	4.35	14.40	10.3	3.1
20	8.18	101.2	2.82	115.2	-1.76	18.6	-1.45	14.02	-0.86	25.12	5.33	13.27	10.0	4.0
21	8.04	26.04	3.6	115.5	-1.71	21.3	-0.88	15.97	0.04	23.54	5.46	15.84	11.9	4.1
22	7.86	160.3	4.4	130.3	0.63	30.1	0.55	17.73	0.71	30.02	7.37	22.73	13.4	4.3
23	8.86	80.77	2.15	113.1	-3	21	-1.52	16.42	-0.02	21.42	7.40	13.60	10.6	5.8
24	8.66	111	2.95	127.8	-0.24	25.85	-0.37	15.83	-0.13	26.46	5.42	20.43	12.5	3.3
25	7.89	434.1	2.8	120.5	-0.9	22.35	-0.68	15.39	-0.21	24.11	6.64	15.71	10.8	4.6
Mean ±SD	**8.54 ±0.68**	**222.65 ±220.28**	**3.13 ±0.54**	**122.29 ±8.05**	**-1.18 ±0.90**	**28.22 ±8.13**	**-0.21 ±0.95**	**18.58 ±3.81**	**0.66 ±1.06**	**30.28 ±7.40**	**8.83 ±4.38**	**19.39 ±4.44**	**12.8 ±2.48**	**5.8 ±1.77**
Median	**8.56**	**107.30**	**3.15**	**123.60**	**-1.01**	**27.35**	**-0.37**	**17.40**	**0.50**	**29.11**	**7.37**	**20.43**	**13.0**	**4.8**
SE	**0.14**	**44.06**	**0.11**	**1.61**	**0.18**	**1.63**	**0.19**	**0.76**	**0.21**	**1.48**	**0.88**	**0.89**	**0.35**	**0.50**

Table 1: Descriptive statistics for age, DHEA-S levels, anthropometrics, and body composition variables

Pubertal Development Scale

Results from the PDS would appear to confirm that very few girls had experienced the adrenarcheal transition judging from the responses to changes in girls' physiology that are associated with adrenarche, despite the wide age range of the participants. For example, only one girl was reported to have axial hair (Table 2), and only four had a distinctive body odor. All the girls in our sample who showed any breast development (n=11) were overfat (body fat percentage >85th percentile, p=0.003).

Pubertal stage	Characteristic	Stage of development: Not yet started	Barely started	Definitely underway	Median age 'barely started' or 'yes'*
Adrenarche	Oily skin	21-no	5-yes		8.57±0.80
	Odour change	20	4	1	8.70±0.50
	Acne	24-no	1-yes		8.71
	Body hair	24	1 (axillary)	0	9.30
Gonadarche	Growth spurt	13	10	2	8.76±0.89
	Breast growth	14	9	2	8.91±0.56

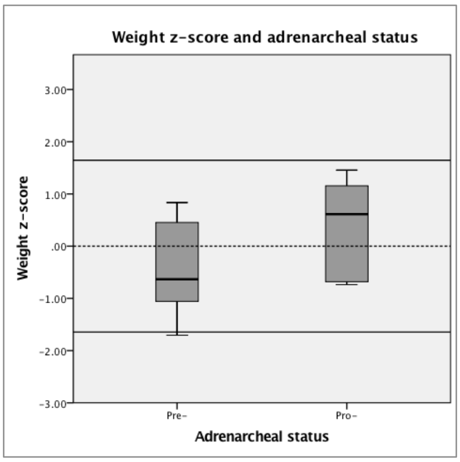
Table 2: Pubertal characteristics of 25 Maya girls in Merida, Mexico, as reported by the mother, and the median age of girls with early breast development

- *Equivalent to Tanner Stage 2.*

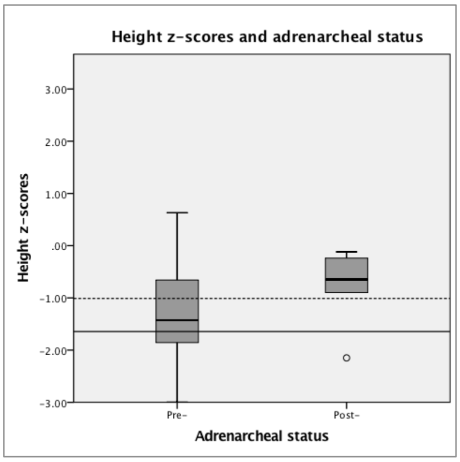
Adrenarche and Anthropometrics

Weight measured at time of saliva collection was significantly associated with adrenarcheal status (U=23.00, p=0.030). However, although the z-score median for weight of the pre-adrenarcheal girls was lower than that of post-adrenarcheal girls (Figure 2A), there was no statistically significant association with adrenarcheal status (p=0.141). Of the ten stunted girls in the sample, only one (currently aged 9.12) had undergone adrenarche; thus, 90% of the stunted girls were pre-adrenarcheal (Figure 2B). Neither height, measured as a continuous variable, or being stunted was significantly associated with adrenarcheal status. Overweight (>85th percentile for BMI z-scores) affected 32% and 50% of pre- and post-adrenarcheal girls, respectively (Figure 2C). Similarly, half of the post-adrenarcheal girls, but only one of five of the pre-adrenarcheal girls were obese (> 95th percentile weight-for-height adjusted for age). No measure relating to weight or body weight status had a significant association with adrenarcheal status.

(A)



(B)



(C)

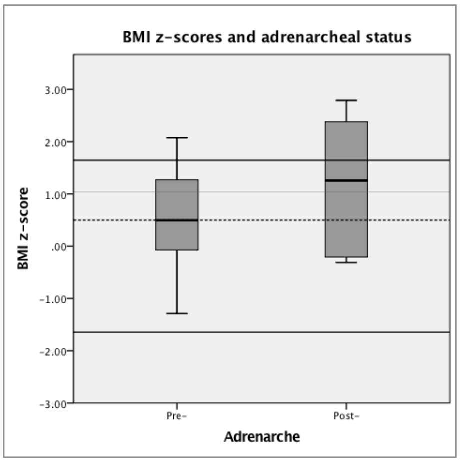
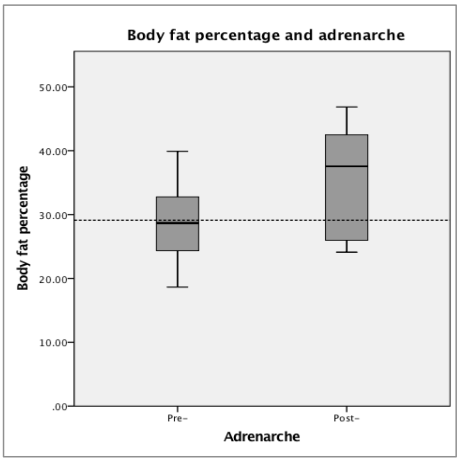


Figure 2A-C: Weight-for-age, height-for-age, and BMI-for-age z-scores plotted against adrenarcheal status in 25 Maya girls from Merida, Mexico. 2A: The dashed line indicates the sample median weight z-score of -0.37, whereas the black lines indicate the 5th and 95th percentile cut-off for weight z-scores. 2B: The sample median height z-score of -1.01 is indicated using a dashed line, whereas the black line indicates the 5th percentile cut-off for stunting. 2C: The black lines indicate the 5th (wasting) and 95th (obesity) percentile cut-offs, whereas the light grey line indicates the 85th percentile (overweight).

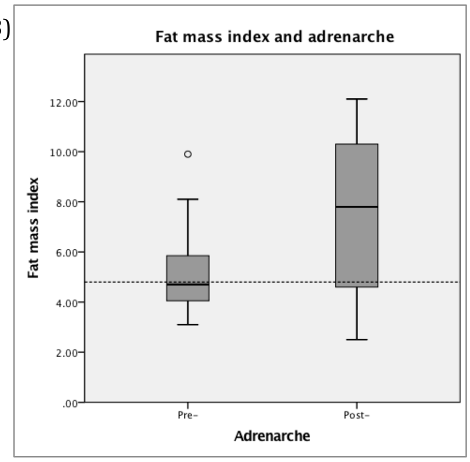
Adrenarche and Adiposity Indicators

A higher proportion of post-adrenarcheal girls (66%) was above the sample median body fat percentage of 29%, compared to pre-adrenarcheal girls (42%) (Figure 3A). Similarly, 66% of post-adrenarcheal girls were above the sample median of 4.80 kg for fat mass index compared to 42% of pre-adrenarcheal girls (Figure 3B), but none of these associations was significant. No clear pattern between the fat free mass index and adrenarcheal status emerged.

(A)



(B)



(C)

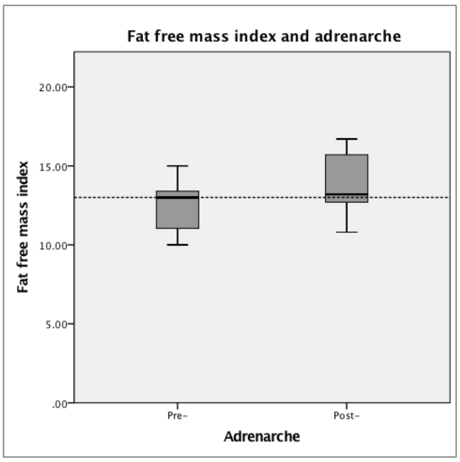


Fig. 3A-C: Body fat percentage (calculated using Lohman et al. 1988), as well as fat mass index and fat free mass index (both calculated using Ramirez et al. 2012) plotted against adrenarcheal status in 25 Maya girls from Merida, Mexico. 3A: The dashed line indicates the sample median body fat percentage of 29.11%. A percentage of 25% indicates obesity. 3B: The sample median fat mass index of 4.8 kg/h^2 is indicated using a dashed line. 3C: The dashed line indicates the sample median fat free mass index of 13.0 kg/h^2.

Adrenarche and birth weight

None of the post-adrenarcheal girls met the WHO criterion for low birth weight, whereas two pre-adrenarcheal girls were born with low birth weights. Using the median birth weight just for this sample of girls (3.15 kg), a greater proportion of pre-adrenarcheal girls was of lower birth weight compared to post-adrenarcheal girls (58% vs 20%) (Figure 4). However, no statistic related to birth weight, whether a continuous or binary variable, showed a statistically significant relationship with adrenarcheal status.

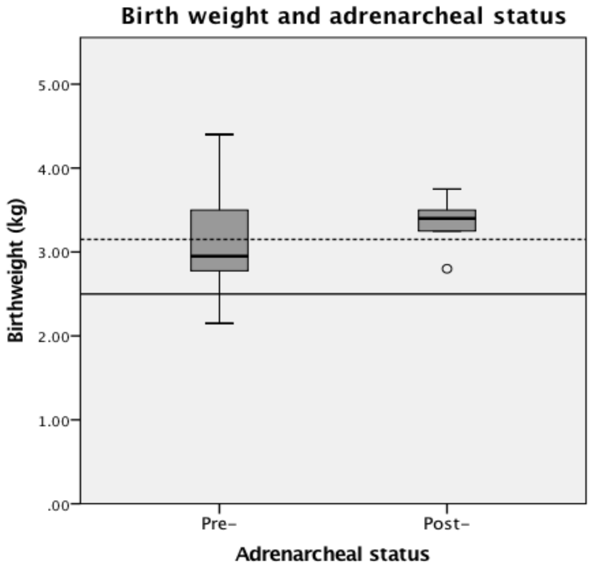


Figure 4: Birth weight (kg) plotted against the adrenarcheal status of 25 Maya girls from Merida, Mexico. The dashed line indicates the sample median of 3.15 kg. The black line at 2.5 kg indicates the WHO definition for low birth weight.

DISCUSSION

As discussed previously, adrenarche has rarely been studied among non-industrialized populations and little is known about normal variation in age at adrenarche among human populations living in diverse ecological settings. The girls who participated in this pilot study were from Merida, the capital of the Yucatan peninsula in Mexico, and were descendants of native Maya living in Mexico at the time of the European conquest. The Maya now rank among the lowest socioeconomic groups in Mexico and have been subject to marginalization and episodes of adversity, e.g. forced labour, land appropriations, and epidemics of infectious diseases, compared to the populations of European origin (Bogin et al., 2007; Leatherman and Goodman, 2005; Varela-Silva et al., 2009). Despite gradual improvements in living conditions (Azcorra et al., 2017; Gurri et al., 2001), many children still suffer from childhood stunting (15.8% for children aged <5 years in the southern region) and poor rates of growth (ENSANUT 2012; Gurri, Pereira, and Moran 2001; Fernald 2007). More recently, as Maya populations have been exposed to globalization, including foods that are high in both sugars and saturated fats, overweight and obesity have become prevalent (31.5% overweight and 13.4% obesity for children aged 5-11 in the southern region of the country) (Azcorra, Wilson, et al. 2013;

ENSANUT 2016, 2012) leading to a dual burden of malnutrition (Dickinson et al. 2011; Doak et al. 2005; Wilson 2011; Bogin, Dickinson, et al. 2018), although only one of the girls included in this sample fell into this category.

Given the temporal association of adrenarche with the BMI rebound and the rapid increase in proportions of overweight/obesity with the nutrition transition in Mexico, we hypothesised that the Maya girls under study here would experience adrenarche at an earlier age than the medians published in most of the literature about adrenarche in healthy groups from high income countries. However, this hypothesis was rejected since the Maya girls reached adrenarche between 8-9 years, closer to the ages reported for the Aka, Ngandu and Sidama populations who occupy more marginal environments (Helfrecht et al., 2017). As previously stated, the timing of adrenarche appears closely related to measures of body composition and energetic status (Ong et al. 2004; Remer and Manz 1999), although a causal relationship between body composition and adrenarche is disputed (Bogin, 2020). Here, the association of adrenarcheal status with most of the age-adjusted anthropometric, standardized measurements was not significant and obvious patterns of association (regardless of statistical significance) were not present in the data, although this may simply reflect the small sample size in this pilot study. Overall, from our data girls with a higher weight- or height-for-age were more likely to have undergone adrenarche compared to their lower weight-for-age or height-for-age peers. However, this may simply reflect the fact that taller and heavier girls were older. Furthermore, a greater percentage of post-adrenarcheal girls were overweight, obese, or overfat compared to their pre-adrenarcheal peers, although there was no statistically significant association between any of these variables. Although being overfat was also significantly associated with reports of breast development, the excess fatness of daughters may have confused mothers' assessments of their daughters' breast status (Wilson 2011:71).

Limitations of the Study

This pilot study was opportunistic, taking advantage of an ongoing research project looking into the dual burden of nutrition among Maya girls aged 7-9, meaning the design was not necessarily optimised for a study of adrenarche. Nevertheless, we were able to take advantage of a large dataset of variables concerning body composition to complement DHEA-S measurements. The sample size was modest, prohibiting multivariate statistics that could have controlled for some covariates, particularly age. By this we mean that given the apparent late age at adrenarche among the Maya girls, the age range of the sample was smaller than ideal and the majority of the sample were pre-adrenarcheal using clinical definitions. Using a larger sample of Maya girls could confirm with greater certainty whether adrenarche occurs at a later age than in healthy, wealthier populations, and also whether the DHEA-S cut-off for adrenarche should be set at a lower concentration compared to standardized values derived from children living in more affluent settings. Future studies of adrenarche in children in settings comparable to the Maya should include a larger number of girls (and boys) of older ages. Inclusion of post-pubertal adolescents could also help to clarify any association (or lack thereof) between adrenarche and puberty.

CONCLUSION

Based on our pilot study presented here, we can confirm (as suggested by other studies among populations living in marginal settings) an apparently wider variation for age at adrenarche than documented in the current biomedical literature. The growing corpus of later mean ages for adrenarche would collectively push the boundaries of adrenarcheal age to one or more years later relative to children in well-nourished, affluent settings, and suggests that the childhood period of plasticity may be more extensive than once thought. How this later transition between childhood and juvenility then might affect the timing of adolescence and young adulthood requires further analyses of larger cross-sectional and longitudinal data sets.

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