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Early BMI Gain and Later Height Growth Predicts Higher DHEAS Concentrations in 7-Year-Old Chilean Children

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Keywords
BMI growth · Linear growth · DHEAS

Abstract
Background: Accelerated weight and height gain in infancy have been associated with premature adrenarche. However, the exact tempo of these events remains undefined. Thus, our goal was to assess the relationship between early BMI and height growth in different periods before 7 years of age and plasma DHEAS levels at 7 years of age. ***Methods:*** This is a longitudinal follow-up of participants of the Growth and Obesity Chilean Cohort Study (GOCS) that represents Chilean children from low- to middle-income families. The subjects were 972 children (48% girls) with birth weights of 2,500–4,500 g for whom serial weight and height measurements from birth until 7 years were available. At 7 years of age, we also measured DHEAS, IGF-I, leptin, insulin, and other metabolic markers in serum. The main outcome of interest was plasma DHEAS concentrations at 7 years of age. ***Results:*** At 7 years of age, children with DHEAS >75th percentile of the sample were taller and fatter and presented higher HOMA-IR and IGF-I than their counterparts ($p < 0.05$). Children with higher DHEAS were heavier at 4 years of age and beyond compared to their counterparts (higher BMI [BMI SDS at 4 years: 1.16, 95% CI 1.02–1.29 vs. 0.83, 95% CI 0.76–0.91, $p < 0.001$]) and taller at 7 years of age (height SDS at 7 years: 0.19, 95% CI –0.08 to 0.31 vs. –0.001, 95% CI –0.06 to 0.06, $p < 0.005$). ***Conclusions***: We observed weight and BMI from 2 to 4 years, and height gains from 4 to 7 years were associated with higher DHEAS levels at 7 years.

Introduction

Adrenarche is a developmental process in higher primates resulting from the activation of the zona reticularis of the adrenal gland leading to an increase of the production of the adrenal androgens (DHEA/DHEAS); it is observed only in humans, chimpanzees, and gorillas [1]. The initiation and physiological control of this event as well as the significance for human prepubertal development remain unknown [2].

Premature adrenarche (PA), initially described in 1952 [3], was defined as the increase in adrenal androgen above the age- and sex-specific normal reference range, before the age of 8 years in girls and 9 years in boys. It was considered a benign condition; however, available evidence associates PA with a greater risk to develop metabolic

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syndrome later in life [4]. Thus, it can no longer be considered a benign normal variation [2, 4].

Both accelerated weight and height gain in infancy have been associated with PA. We have recently reported data from a longitudinal study showing that adiposity at the age of 7 years was positively associated with DHEAS [5] and that this effect was only partially explained by changes in IGF-I and leptin. Obese children at 7 years of age (17% of total children in the cohort) had doubled the risk of high DHEAS; furthermore, those with high DHEAS were fatter and more centrally obese than their counterparts. Additionally, it is known that obese children are actually taller than their peers during early childhood [6]. Thus, it is likely that the insulin-leptin-IGF-I system acts to promote longitudinal growth in these children. Utriainen et al. [7] found, in a retrospective analysis of 54 patients with PA, that length SDS increment during the first 2 years of life preceded the increased adiposity assessed by a higher weight-for-height. Currently, the exact temporalities of accelerated linear growth and/or increase in BMI in children who develop PA remain poorly defined. Thus, our aim was to further assess the relationship between changes in early BMI, height growth, and DHEAS concentrations at 7 years in a longitudinal study of Chilean children with birth weights between 2,500 and 4,500 g.

Subjects and Methods

Our study sample was drawn from children enrolled in the Growth and Obesity Chilean Cohort Study (GOCS) that assesses the association of early growth and development with adiposity and metabolic risk [8]. Children were eligible for the study if they met the following criteria: age 3.0–4.9 years; attending Chilean National Nursery School Council Program (JUNJI) nursery schools from the south area of Santiago, Chile, in September 2006; singletons; gestational age 37–42 weeks; birth weight ≥2,500 g (data retrieved from medical registries); and no physical or psychological conditions that could severely affect growth. 85% of these agreed to participate (n = 1,195). No significant differences in age, sex, birth, and anthropometry at 4 years between participants and nonparticipants were noted. Thereafter, annual evaluations have been conducted. In 2009, 1,044 children of the original cohort were evaluated (~87%). For the current analyses, we excluded 36 girls that had presence of breast bud (breast Tanner stage II) at the age of 7 years, 37 children where no blood sample was obtained due to difficulties, 2 children with implausible DHEAS concentrations, and 25 children with incomplete growth data; thus, our final sample size was 972 children. Assuming 80% power and a 2-tail significance level of 0.05, we were able to detect small effect sizes.

The study protocol was approved by the Institutional Review Board of the Institute of Nutrition and Food Technology (INTA) of the University of Chile. Written informed consent was obtained from all parents or guardians of the children.

Child's Anthropometry from 0 to 7 Years and Maternal Height

From 0 to 3 years, weight and height (recumbent length in children younger than 2 years) data were abstracted from health records. The validity of these data has been verified [8]. Thereafter, a dietitian measured weight, height, and waist circumference annually using standardized procedures. At 7 years, a single dietitian carried out all measurements as follows. Weight was measured with a TANITA BC-418 device (Tanita Corp., Tokyo, Japan) with a precision of 0.1 kg; height was measured with a wall-mounted Harpenden stadiometer (Holtain, UK) to the nearest 0.1 cm; waist circumference (i.e. minimum circumference between the iliac crest and the rib cage) was measured with a metal inextensible tape (Lufkin W606PM) to the closest 0.1 cm; and biceps, triceps, as well as suprailiac and subscapular skinfolds were measured in triplicate with a Lange caliper (Scientific Industries, Cambridge, MD, USA) with the capacity to measure up to 67 mm and an accuracy of 0.5 mm; the mean value was used in the analyses. The intraobserver technical error of measurement and the mean average bias of the observer were within the limits suggested by the WHO growth reference study [9].

Clinical Adrenal and Pubertal Development and Bone Age Assessment at 7 Years

A single pediatric endocrinologist (V.M.) assessed breast and genital development by palpation and classified breast and testes according to Tanner stages [10, 11]. The same endocrinologist evaluated the presence of adult-type body odor, oily hair, acne, and sexual hair (axillary and pubic). At age 7 years, we also assessed skeletal maturation of children through commercial ultrasound equipment (BonAge Sunlight Medical®, Tel Aviv, Israel) [12].

Blood Sample at 7 Years

A trained nurse collected a fasting venous sample from the children at arrival to the outpatient clinic of INTA. Mothers were contacted the day before sample drawing to confirm the absence of fever (>37.5°C) or symptoms of acute infection in the children, as well as to advise them not to provide foods or liquids before arriving to the clinic. These conditions were re-checked by the nurse at the time of the blood collection and if not met, exams were rescheduled. Serum glucose and serum triglyceride concentrations were assessed by enzymatic colorimetric techniques (HUMAN; Gesellschaft für Biochemica und Diagnostica, Wiesbaden, Germany) and serum insulin, using a radioimmunoassay kit (Linco Research Inc., St. Charles, MO, USA). HDL cholesterol was measured by selective precipitation with sodium phosphotungstate and magnesium chloride solution [13, 14]. Serum leptin and adiponectin were measured by commercial radioimmunoassay (Millipore). Analyses were conducted at the Nutrition Laboratory of the Catholic University of Chile. This laboratory conducts daily assessments of the accuracy of the measurements by using UNITY quality control software (Bio-Rad Laboratories Inc., Hercules, CA, USA) and, for lipid measurements, has a Certificate of Traceability periodically updated by the Center for Disease Control and Prevention (CDC) [15, 16]. Hormonal analyses were conducted at the Institute of Maternal and Child Research University of Chile. Serum DHEAS was determined by competitive specific binding radioimmunoassay supplied by Diagnostic System Laboratories (Webster, TX, USA); intra- and interassay coefficients of variation were 3.5 and 5.1%, respectively. Serum IGF-I was measured by using a standardized locally developed radioimmunoassay requiring sample extrac-

Table 1. Anthropometric characteristics of 972 Chilean children from 0 to 7 years and hormonal and metabolic status at 7 years

	Years							
	0	1	2	3	4	5	6	7
Subjects, *n*	933	771	724	540	942	944	257	972
Female[a]	445 (48.8)	370 (48.0)	342 (47.2)	256 (47.4)	453 (48.1)	455 (48.2)	110 (42.8)	469 (48.3)
Age, months	0	12.09±0.31	24.2±0.61	36.29±0.67	51.64±4.01	59.98±4.6	71.18±4.13	82.26±5.34
Weight, kg	3.39±0.41	9.83±1.12	12.65±1.5	15.09±1.91	18.15±2.53	19.94±3.09	22.2±3.58	25.15±4.71
Weight-for-age SDS	0.19±0.84	0.41±0.95	0.48±0.96	0.45±0.97	0.47±0.95	0.54±1.01	0.55±1.02	0.66±1.12
Height, cm	49.9±1.71	74.3±2.61	86.33±3.18	94.73±3.52	104.1±4.31	109.11±4.72	114.47±4.69	120.71±5.38
Height-for-age SDS	0.21±0.91	−0.27±1.03	−0.12±1.01	−0.26±0.92	−0.22±0.88	−0.09±0.9	−0.14±0.89	0.05±0.91
BMI	13.61±1.31	9.82±1.12	12.65±1.5	15.03±1.89	18.15±2.53	16.68±1.81	22.2±3.59	17.16±2.33
BMI-for-age SDS	0.13±1.01	0.77±0.99	0.78±1.00	0.84±1.08	0.92±1.02	0.87±1.08	0.90±1.09	0.86±1.16
BMI >2 SDS[a]	3.44 (32)	10.33 (79)	9.37 (67)	12.67 (65)	13.91 (131)	13.79 (134)	12.89 (33)	17.28 (168)
Waist circumference, cm					53.29±3.82	54.76±4.55	55.77±5.16	58.8±6.5
Central obesity[a, b]					6.6 (62)	8 (73)	5.7 (14)	10.3 (97)
Percent fat (Slaughter)								15.76±4.82
Fat mass index BIA, kg/m^2								4.13±1.33
Hormonal and metabolic markers								
DHEAS, μg/dL								35.38±21.76
Glucose, mg/dL								89.59±6.22
Insulin, μg/dL								5.48±1.46
HOMA								1.22±0.37
Total cholesterol, mg/dL								166.74±26.66
LDL cholesterol, mg/dL								97.46±26.64
HDL cholesterol, mg/dL								50.48±13.79
Triglycerides, mg/dL								93.96±43.08
IGF-I, ng/mL								182.25±54.88
IGF-I, *z* score								−0.06±1.04
Leptin, ng/mL								5.81±3.98
Adiponectin, ng/mL								18.02±6.76

Values are mean ± SD, unless otherwise indicated. BIA, bioimpedance analysis.
[a] Estimated parameters are % (*n*). [b] Defined as 90th percentile of waist circumference according to the Mexican-American girls reference of the Third National Health and Nutrition Examination Survey (NHANES III).

tion as a first step (sensitivity: 5 ng/mL; intra- and interassay coefficients of variation: 8.6 and 10.2%, respectively) [17].

Maternal Height and Maternal Age at Menarche

At 7 years, a single dietitian also measured maternal height following standard procedures; the same wall-mounted Harpenden stadiometer (Holtain) was used and measures were recorded to the nearest 0.1 cm. Maternal age at menarche was self-reported by the mother.

Computed Indices

We divided weight (kg) by height squared (m^2) to calculate BMI. We estimated weight-for-age (WAZ), height-for-age (HAZ), and BMI-for-age (BAZ) based on the WHO 2006 standards and the WHO 2007 growth reference [9]. We defined obesity as BAZ ≥2 SD. Adiposity at the age of 7 years was defined as % fat calculated as total fat estimated from biceps and triceps skinfolds using the Slaughter equation [18]. Body fat estimated from bioimpedance analysis was also divided by height squared to calculate fat mass index (FMI = fat/height^2). Central obesity was defined as the 90th percentile of waist circumference according to the Mexican-American girls reference of the Third National Health and Nutrition Examination Survey (NHANES III) [19]. High DHEAS (biochemical adrenarche) was defined as DHEAS concentration based on sample distribution (75th percentile); cutoffs were 42.0 μg/dL for girls and 45.1 μg/dL for boys. The homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5.

Statistical Analyses

We present data as either means (or geometric means) and standard deviations (SD = Z) or frequencies and 95% confidence intervals. We tested differences by DHEAS levels (adjusted by sex and age at sampling collection) using the Student *t* test for continuous variables or the χ^2 and Fischer test for dichotomous variables. Growth was divided in 4 periods of interest based on the literature: prenatal (i.e. 0 years), 0–2, 2–4, and 4–7 years. We used linear regression models to assess the relative contribution of each of these periods of growth on DHEAS concentrations at 7 years. In these analyses conditional changes of anthropometrical measurements were used rather than raw data to avoid correlation between subsequent growth measurements and regression to the mean effect; results were expressed as SD to allow for comparisons across indices. Generalized linear models served to assess the risk of high DHEAS of children with birth weight <3,000 g and birth length <48 cm. Interactions by sex were all nonsignificant; thus, results

Table 2. Anthropometric, hormonal, metabolic, and maternal antecedents in 972 Chilean children by DHEAS concentrations at 7 years of age adjusted by age and sex, except for those variables with an asterisk

	DHEAS ≥75th percentile	DHEAS <75th percentile	*p* value
DHEAS, μg/dL	64.91±20.21	25.22±9.59	
Subjects, *n*	249	723	
Female[a]	47.79 (119)	48.41 (350)	ns*
Chronological age, months	83.58±5.05	81.81±5.36	<0.01*
Bone/chronological age	1.17±0.14	1.13±0.14	<0.01
Anthropometry			
Weight, kg	25.46±1.2	25.05±1.28	<0.01
Weight-for-age SDS	1.02±1.15	0.54±1.08	<0.01*
Height, cm	121.3±2.27	120.51±2.42	<0.01
Height-for-age SDS	0.198±0.9	–0.001±0.9	<0.01*
BMI	17.21±0.17	17.15±0.19	<0.01
BMI-for-age SDS	1.24±1.21	1.12±1.2	<0.01*
BMI >2 SDS[a]	26.7 (64)	14.6 (103)	<0.01*
Waist circumference, cm	59.12±1.15	58.71±1.23	<0.01
Central obesity[a, b]	17.5 (42)	7.8 (55)	<0.01
Percent fat (Slaughter)	15.89±0.97	15.71±0.97	ns
Fat mass index BIA, kg/m^2	4.15±0.18	4.11±0.18	ns
Hormonal and metabolic markers			
Glucose, mg/dL	89.73±0.89	89.54±0.03	ns
Insulin, μg/ dL	5.5±0.1	5.48±0.1	ns
HOMA-IR	1.223±0,024	1.215±0,025	<0.01
Total cholesterol, mg/dL	166.89±1.78	166.7±1.76	ns
LDL cholesterol, mg/dL	97.34±1.84	97.5±1.87	ns
HDL cholesterol, mg/dL	50.75±1.02	50.39±1.08	<0.01
Triglycerides, mg/dL	93.93±0.33	93.96±0.33	ns
IGF-I, ng/ml	181.84±7.08	182.38±7.02	ns
IGF-I, *z* score	0.12±1.14	–0.13±1.00	<0.01*
Leptin, ng/ml	5.8±0.09	5.81±0.09	ns
Adiponectin, ng/mL	18±0.34	18.03±0.34	ns
Mother			
Maternal height, cm	157.3±6.09	156.9±6.54	ns*
Maternal age at menarche, years	13.4±7.6	13.6±8.9	ns*

Values are mean ± SD, unless otherwise indicated. BIA, bioimpedance analysis; ns, nonsignificant.
[a] Estimated parameters are % (*n*). [b] Defined as 90th percentile of waist circumference according to the Mexican-American girls reference of the Third National Health and Nutrition Examination Survey (NHANES III).

are presented for both sexes combined. All analyses were adjusted for age, sex, maternal height, and age at menarche. Associations were considered significant if $p < 0.05$. Analyses were carried out using SAS (version 9.1; SAS Institute, Cary, NC, USA).

Results

A total sample of 972 children (503 boys and 469 girls) with a mean age of 6.9 years was evaluated. Mean BMI exceeded WHO standards from birth onwards (0.87 BMI SDS at 7 years), while height was slightly below until 6 years and increased thereafter (0.05 height SDS at 7 years). At 7 years, mean DHEAS concentrations were 29.7 ± 1.59 μg/dL and did not differ by gender (Table 1). None of the children presented clinical evidence of pubarche.

At 7 years, children with high DHEAS (>75th percentile) presented more advanced bone maturation and were significantly taller and fatter than their counterparts ($p < 0.05$; Table 2). They also had higher concentrations of IGF-I, HOMA-IR, and HDL cholesterol ($p < 0.05$) adjust-

ing by age and sex. Maternal height and maternal age at menarche were also similar for both groups.

Low-birth-weight and premature children were excluded by design of this cohort; however, the prevalence of newborns with birth weight <3,000 g was 15.4% (n = 37) in the children with higher DHEAS and 20.1% (n = 120) in those with lower DHEAS at 7 years.

Growth comparison between children with higher and those with lower DHEAS concentrations at 7 years shows that the children with higher DHEAS have no differences in weight, length, and BMI at birth, or at 2 years, but have higher weight and BMI SDS from 4 years on ($p < 0.05$) and higher height only at 7 years of age (Fig. 1).

Weight, BMI, and length at birth were not associated with DHEAS at 7 years after adjusting for age, sex, maternal height, and maternal age at menarche ($p > 0.05$). Weight, BMI, and height gains from 2 to 4 years and from 4 to 7 years were associated with higher DHEAS levels at 7 years (Fig. 2).

Furthermore, logistic models adjusted for sex, age, maternal height, and maternal age at menarche were performed, showing that children with birth weight <3,000 g and birth length <48 cm had no increased risk of higher DHEAS (data not shown).

Sensitivity Analyses

Analyses including girls who have already started puberty (n = 36) did not result in meaningful changes of the results both in terms of direction and effect sizes.

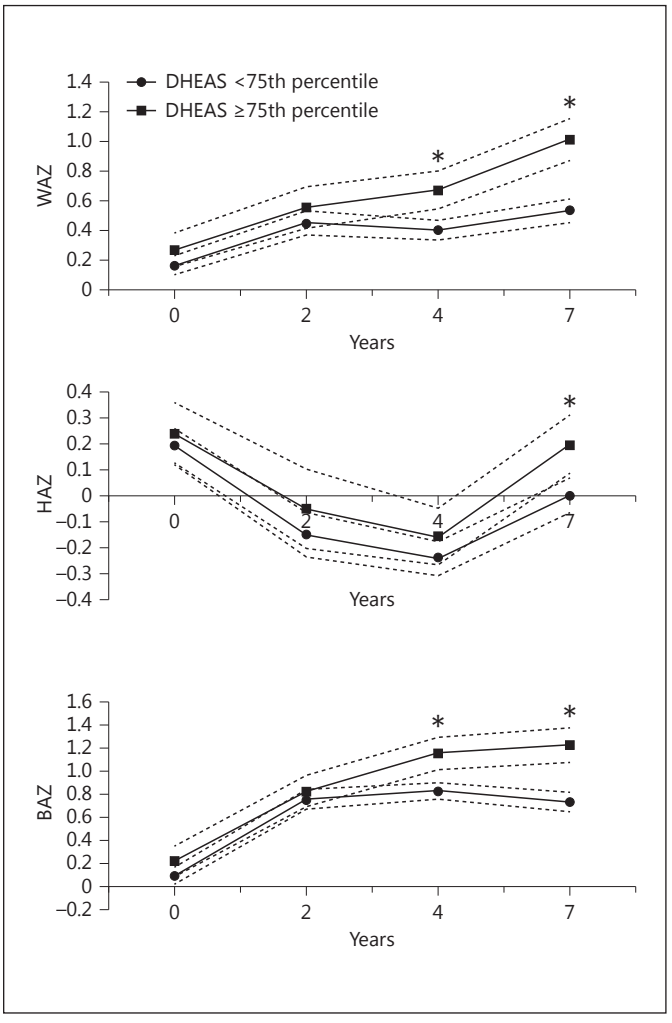

Fig. 1. Mean and 95% CI for weight-for-age (WAZ), height-for-age (HAZ), and BMI-for-age (BAZ) SDS from 0 to 7 years in Chilean children by DHEAS concentrations at 7 years of age. DHEAS >75th percentile was defined according to sample distribution: 42.0 μg/dL for girls and 45.1 μg/dL for boys. Anthropometric SDS based on WHO 2006 and WHO 2007 standards. * $p < 0.05$.

Discussion

In this longitudinal sample of term-born children of normal birth weight recruited from the community, we observed that increased weight gains and increased linear growth between 2 and 4 years and thereafter were associated with increased DHEAS at 7 years. The children with higher DHEAS at 7 years reached significantly higher weight SDS (≈0.3) by 4 years of age compared to those with lower DHEAS, while significantly higher height SDS (≈0.2) was detected only at 7 years. Thus, with respect to early (biochemical) adrenarche in normal-birth-weight children, the timing of growth events appears to be increased weight gain preceding and probably contributing to subsequent linear growth.

We defined adrenarche based on DHEAS concentrations only. Interestingly, despite the high DHEAS concentrations observed in our sample, none of the children presented clinical signs of pubarche. This is consistent with the fact that Amerindian populations present less pubic hair and delayed pubarche when compared to other races [20, 21]. In fact, clinical signs of adrenarche are not correlated with the presence of adrenal androgen levels and appear to be a sexually dimorphic process [22], with a lower percent of boys showing clinical signs. Thus, the conversion of adrenal androgen precursors to potent androgens or the activation of the androgen receptor is sexually dimorphic, and our results suggest that they are also ethnic dependent, perhaps due to variability in the androgen receptor activity in the target tissues.

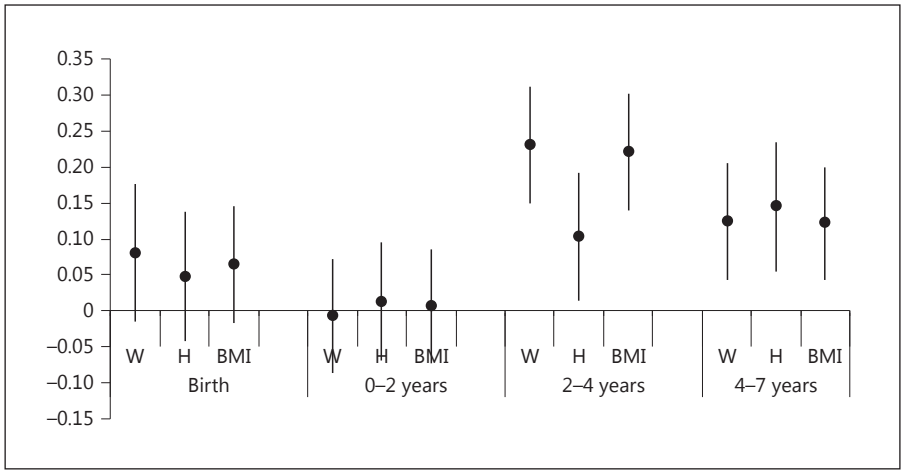

Fig. 2. Standardized regression coefficients (95% CI) for DHEAS concentration at 7 years of age at birth and per sample-specific 1-SD increments in weight, length, and BMI changes from 0–2, 2–4, and 4–7 years (n = 751). W, weight; H, height; BMI, body mass index. All analyses were adjusted for previous period of growth, sex, age, maternal age at menarche, and maternal height.

We found that increased weight gain in childhood was positively related to DHEAS concentrations at 7 years. This finding is again in line with the findings of the ALSPAC follow-up, which showed that rapid weight gain between 0–3 years was associated with higher adrenal androgen levels at 8 years [23]. This is also consistent with the observation that BMI gains correlate with DHEAS increases [24]. In our study, the increased weight gain in infancy was followed by a later increase in linear growth during childhood. Opposite temporality of events was described in a case control study of girls with PA [7]; however, the latter study defined PA based on the presence of clinical signs and, therefore, considered a more restricted clinical sample.

Growth effects may be mediated by insulin, IGF-I, and leptin. Two studies have previously demonstrated that insulin concentrations increase independently of weight in girls with PA [4, 25], but this finding was not corroborated by others [5, 26]. In the present study we found a significantly higher HOMA-IR in children with high DHEAS at 7 years. In mice, the addition of insulin to the culture medium of metatarsal bones induced the metatarsal linear growth and increased their growth plate height. In addition, insulin stimulated cultured chondrocyte proliferation and differentiation, with both effects being prevented by transfection with a small interfering RNA targeted to the insulin receptor. These results suggest that insulin has direct effects on linear growth. [27]. In addition to a higher HOMA-IR, we found a same direction differences in IGF-I concentrations. The key role of nutrition in modulating liver IGF-I and pancreatic insulin secretion is observed early on in life. In a cohort of children born small for gestational age, rapid weight gain during infancy was associated to higher insulin and IGF-I as early as the first year [28]; the ALSPAC study also reported a relationship between rapid infant growth and IGF-I at 5 years [29]. IGF-I promotes increased linear growth through direct and indirect effects [30, 31]. Thus, we hypothesize that increased weight gain leads to increases in insulin and IGF-I concentrations, which in turn stimulate linear growth.

In our study, we did not find that a smaller size at birth, defined either in terms of weight or length, is associated with higher DHEAS at 7 years of age. Ibanez and coworkers proposed a connection between a history of small for gestational age and premature pubarche [32] as well as between low birth weight and the outcome of premature pubarche [33]. In our cohort, by design, we did not include small-for-gestational-age infants, but we observed that those born with a birth weight <3 kg or with a birth length <48 cm had no increased risk of high DHEAS at 7 years. Our findings are in line with our own experience in early pubertal girls of low birth weight gain and with other groups which have not demonstrated this association [7, 34–36].

The physiological role of adrenarche and its implications for future health are not well defined, but the identification of nutritional status as being the first event determining PA suggest the possibility to prevent this by carefully designed clinical interventions. From the evolutionary perspective, it has been suggested that adrenarche is a key component of "juvenility," serving the adaptation of body composition and metabolic status to environmental conditions [37]. A second interesting hypothesis refers to the neuromodulatory effects of DHEAS in support of brain maturation in prepubertal children [38].

There is also a continuing debate with regard to the dependency of adrenarche and puberty on the physiological situation. Children with PA have earlier transient prepubertal growth acceleration, significantly advanced bone age [26], higher diaphyseal bone strength, and higher body fat mass [39, 40]. In a Catalonian cohort, girls with PA had increased risk of earlier puberty [41] and functional ovarian hyperandrogenism [42]. However, final height and subsequent developmental milestones like puberty do not appear significantly affected in children with PA in other reports [43–45]. As we continue to follow up these children, our cohort may yield further data to help elucidate these issues.

Conclusions

Our findings have contributed in establishing that in children with normal birth weight and higher DHEAS at 7 years we observe increased weight and height growth from 2 years on that result in higher weights from 4 years on and higher height at 7 years. Longitudinal follow-up of these children may allow us to identify whether high DHEAS at 7 years heralds any significant differences with respect to metabolic consequences for one or both sexes, pubertal timing and progression, gonadal function, and whether there is an intrinsic risk linked to early adrenarche separate from that derived from routine indices of nutritional status.

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Disclosure Statement

The authors declare that they have no financial competing interests. The sponsor had no involvement in any of the phases of the study or in the writing of this paper.

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