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Tracking of Serum DHEAS Concentrations from Age 1 to 6 Years: A Prospective Cohort Study

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Context: Adrenarche is a gradual process, but its programming is unknown.

Objective: The objective of this article is to examine the trajectory of dehydroepiandrosterone sulfate (DHEAS) from age 1 to 6 years and the associations of early growth with DHEAS concentration by age 6 years.

Design and participants: Longitudinal data from a population sample of 78 children (43 girls) with serum samples for DHEAS and insulin-like growth factor 1 (IGF-1) measurements available at ages 1 and 6 years.

Main outcome measure: Serum DHEAS concentration at age 6 years.

Results: DHEAS concentration at age 1 year correlated with DHEAS concentration at age 6 years ($r = 0.594$, $P < .001$). DHEAS levels at age 6 years increased with tertiles of DHEAS at age 1 year (medians (μg/dL); 4.2, 14.4, 22.6; $P < .001$) and with those of greater increase in length by age 1 year (6.0, 11.7, 16.4; $P = .047$), and decreased with tertiles of birth length (17.7, 13.3, 7.1; $P = .042$). In a regression model including birth size, biochemical covariates at age 1 year, and growth measures by age 6 years, higher DHEAS concentration at age 1 year was an independent determinant of falling into the highest DHEAS tertile at age 6 years.

Conclusions: Higher serum DHEAS concentrations already at age 1 year are associated with those at age 6 years. Also, shorter birth length and rapid catch-up growth in length by age 1 year are associated with higher DHEAS concentrations at age 6 years. These results corroborate the early origin of adrenarche and strongly suggest that part of adrenarchal programming already takes place by the end of infancy.

Key Words: adrenarche, birth size, growth, dehydroepiandrosterone sulfate, insulin-like growth factor 1

Abbreviations: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; IGF-1, insulin-like growth factor 1; IQR, interquartile range; OR, odds ratio; SD, standard deviation; SDS, standard deviation score.

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Adrenarche refers to a progressive increase of adrenal androgen secretion in mid-childhood that results from the maturation of the adrenocortical zona reticularis [1]. Dehydroepiandrosterone sulfate (DHEAS), secreted from zona reticularis of the adrenal cortex, is a surrogate marker of adrenal androgen production. DHEAS and other adrenal androgen products, dehydroepiandrosterone and androstenedione, act as precursors for peripheral cells that can convert them to androgens with a capability to activate the androgen receptor [2]. Adult-type body odor, greasiness of skin and hair, acne, and growth of axillary and pubic hair are the clinical signs of androgen action [1].

Previous studies have shown that adrenal androgen secretion in mid-childhood is associated with early life factors such as nutritional status and early growth, including birth size. Low birth weight or being born small for gestational age have been associated with higher adrenal androgen secretion in mid-childhood [3], especially when followed by rapid early catch-up growth or weight gain [4, 5]. Also, increased weight gain and linear growth later in childhood [6, 7], and increased adiposity and higher intake of several nutrients [8, 9] have been linked with higher DHEAS levels in mid-childhood. Similarly, the secretion pattern of insulin-like growth factor 1 (IGF-1) seems to be programmed in early childhood because circulating IGF-1 levels at prepubertal age are associated with birth size and early growth rate [10]. On the other hand, several studies have demonstrated that children with premature adrenarche have increased growth in length/height and weight gain already in the first years of life [11, 12], and they tend to have higher circulating IGF-1 levels in childhood compared to their peers [11, 13].

Although growing evidence suggests that early growth modifies gradual adrenal maturation, it is not well known at which age the patterns of adrenal androgen secretion are programmed and if early serum DHEAS levels are associated with DHEAS concentrations in later childhood. We hypothesized that the patterns of adrenal androgen secretion are programmed already by the end of infancy, and therefore our main aim was to investigate the associations of DHEAS at age 1 year and early growth with serum DHEAS concentrations in mid-childhood at age 6 years. Additionally, because IGF-1 has close associations with linear growth [14] and adrenarche [13, 15], we investigated serum IGF-1 concentrations at age 1 and 6 years in relation to growth and DHEAS measures.

1. Participants and Methods

A. Participants and Design

A sample of 78 children (43 girls) in the present study were originally the participants of the Finnish LUKAS birth cohort studies recruited from September 2002 to May 2004 [16]. LUKAS1 cohort is a Finnish part of the European birth cohort study PASTURE (Protection against Allergy Study in Rural Environments) [17] among farmers and nonfarmers, whereas the second half of the cohort (LUKAS2) consists of unselected children [16]. All children without any long-term medication and with data on DHEAS and IGF-1 measurements available both at ages 1 and 6 years were included in the present study. Ethical approval of this study was granted by the research ethics committee of the Hospital District of Northern Savo (Kuopio, Finland). Written consent forms were obtained from the parents of the participating children.

B. Clinical Assessment

Birth measures were recorded by midwives working on labor wards and measured with standardized infantometers and calibrated scales to the accuracy of 0.1 cm and 0.01 kg, respectively. If necessary, birth measures were supplemented later from the records of local child health centers. All anthropometric measures were recorded by a trained nurse, as part of the routine health check-up in local child health center at age 1 year and by the research team at age 6 years. Length at age 1 year was measured using a standardized infantometer and height at age 6 years by a wall fastened stadiometer (Bodymeter 206, Seca), both to the accuracy of

0.1 cm. Weight was measured using a calibrated electric scale to the accuracy of 0.1 kg. The appearance of androgenic signs was questioned by a structured questionnaire of the parents and verified by clinical examination at age 6 years. Adult-type body odor was recorded if the parents reported a clear change in the type of axillary odor and/or a frequent need for antiperspirant, or if axillary adult-type odor and wetness were present in the clinical examination. Greasiness of hair was recorded if the parents reported a clear greasiness of hair and/or need for daily hair wash. Tanner pubertal stage [18, 19], axillary hair, acne, and comedones were evaluated by a trained nurse in systematic examination. Testicular volumes were estimated with an orchidometer. According to Tanner stage, all children were prepubertal. Children with at least one of the following androgenic signs were considered to have clinical adrenarche: adult-type body odor, greasiness of hair, comedones/acne, and pubic or axillary hair. Biochemical adrenarche was defined as serum DHEAS concentration greater than or equal to 40 μg/dL (1.08 μmol/l), which is above average for prepubertal children age 6 to 8 years [11].

C. Biochemical Analyses

Blood samples were drawn and serum samples for DHEAS and IGF-1 measurements were stored at –80°C until assayed. We measured serum DHEAS and IGF-1 concentrations using enzyme-linked immunosorbent assays with a Bio-Rad model 550 microplate reader (Bio-Rad Laboratories Inc) and specific kits (DHEAS, cat 1950, Alpha Diagnostic, International [20]; IGF-1, cat E20, Mediagnost [21]). For DHEAS, the intra-assay and interassay coefficients of variation were 11.2% and 7.6%, respectively. For IGF-1, the corresponding values were 11.1% and 10.6%. The detection limit was 0.5 μg/dL for DHEAS and 20 ng/mL for IGF-1.

D. Computed Indices

All anthropometric SD scores were calculated using the current Finnish references [22, 23]. Regarding birth size, infant growth (Δlength and Δweight-for-length SD score from birth to age 1 year), later childhood growth (Δheight and Δweight-for-height SD score from ages 1 to 6 years), and age 1 year biochemical levels, the children were divided into tertile groups (depicted as 1 to 3 in Figs. 1 and 2, one indicating the lowest tertile). The tertile groups were defined by dividing an equal number of participants to each of 3 tertiles. The ranges within each tertile for these parameters were as follows:

Birth length SD score: –1.90 to –0.40, –0.39 to 0.39, and 0.40 to 1.90;
Birth weight SD score: –2.00 to –0.40, –0.39 to 0.39, and 0.40 to 2.30;
ΔLength SD score from birth to age 1 year: –2.44 to –0.81, –0.80 to 0.07, and 0.08 to 2.22;
ΔWeight-for-length SD score from birth to age 1 year: –2.84 to –0.92, –0.91 to 0.01, and 0.02 to 2.57;
Serum DHEAS concentration (μg/dL) at age 1 year: 0.2 to 1.4, 1.5 to 3.8, and 3.9 to 27.6;
Serum IGF-1 concentration (ng/mL) at age 1 year: 32.3 to 59.4, 59.5 to 86.3, and 86.4 to 184.8;
ΔHeight SD score from ages 1 to 6 years: –3.08 to –0.23, –0.22 to 1.11, and 1.12 to 3.42; and
ΔWeight-for-height SD score from ages 1 to 6 years: –2.22 to –0.24, –0.23 to 0.61, and 0.62 to 2.74.

E. Statistical Analyses

We performed all statistical analyses using SPSS 24.0 software (IBM Corp). Differences between the groups with P less than .05 were considered significant. The normality of the distributions for all continuous variables were first inspected visually from the histograms and using the Shapiro-Wilk test. Correlations between the studied parameters were analyzed using the Spearman rank order correlation test. To compare the differences between sexes, we used the independent samples t test or the Mann-Whitney U test for

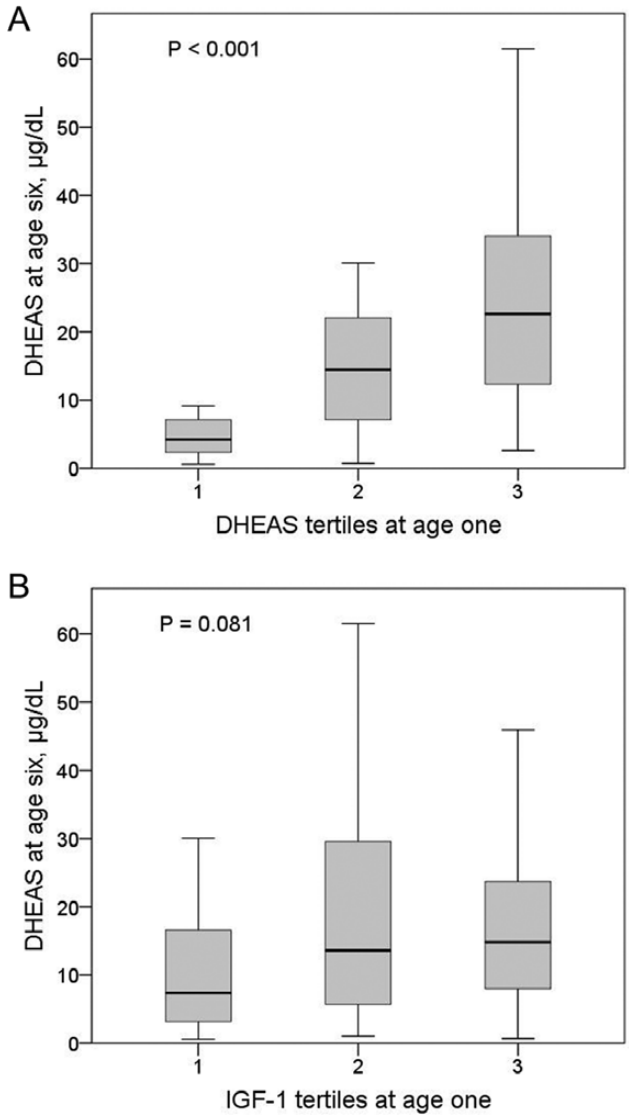

Figure 1. Serum dehydroepiandrosterone sulfate (DHEAS) concentrations (µg/dL) at age 6 years in the 78 children of the study by A, DHEAS and B, insulin-like growth factor 1 (IGF-1) tertiles at age 1 year (group 1 indicating the lowest tertile). Horizontal solid lines depict medians, gray boxes represent interquartile ranges (IQR), and whiskers indicate variability outside the upper and lower quartiles. Differences between the tertile groups were analyzed using the Kruskal-Wallis test. Median (IQR) serum DHEAS concentration (µg/dL) in each tertile, respectively: A, by DHEAS tertiles at age 1 year, 4.2 (2.3-7.6), 14.4 (6.9-22.1), and 22.6 (12.0-36.2); and B, by IGF-1 tertiles at age 1 year, 7.4 (3.1-17.0), 13.6 (5.6-30.1), and 14.8 (7.5-24.4). Conversion multiplier to SI units: DHEAS, µmol/l = µg/dL × 0.0271.

continuous variables, and χ^2 test for categorical variables. When analyzing differences between the tertile groups, we used the Kruskal-Wallis test. Determinants of falling into the highest DHEAS tertile at age 6 years were analyzed using binary logistic regression models. Continuous nonnormally distributed covariates in the regression model were first logarithmically transformed and then used as SD scores as continuous variables.

3. Results

Characteristics of the children at birth, at age 1 year, and at age 6 years are shown in Table 1. One girl and 2 boys had been born slightly preterm (at the gestational age of

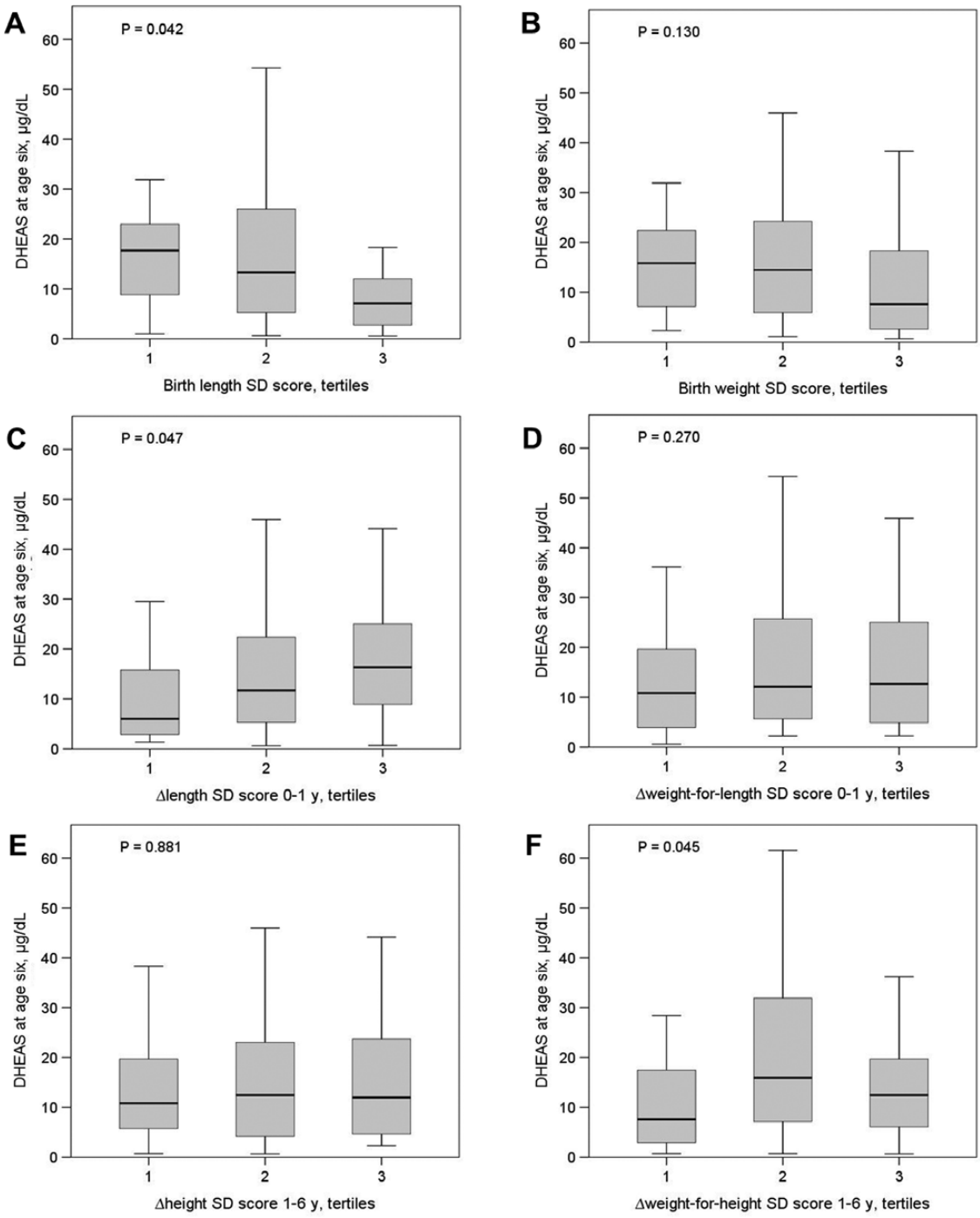

Figure 2. Serum dehydroepiandrosterone sulfate (DHEAS) concentration (µg/dL) at age 6 years in the 78 children of the study by A and B, birth size, and C and D, growth from birth to age 1 year, or E and F, from age 1 to 6 years. For each studied variable, children were divided into tertile groups, with group 1 indicating the lowest tertile. Horizontal solid lines depict medians, gray boxes represent interquartile ranges (IQR), and whiskers indicate variability outside the upper and lower quartiles. Differences between the tertile groups were analyzed using the Kruskal-Wallis test. Median (IQR) serum DHEAS concentrations (µg/dL) in each tertile, respectively: A, by birth length SDS tertiles, 17.7 (8.2-23.2), 13.3 (4.9-26.4), and 7.1 (2.7-14.1); B, by birth weight SDS tertiles, 15.8 (6.5-22.7), 14.4 (5.7-25.7), and 7.6 (2.5-20.8); C, by Δlength SDS 0-1y tertiles, 6.0 (2.8-18.4), 11.7 (4.8-22.4), and 16.4 (8.6-25.2); D, by Δweight-for-length SDS 0-1y tertiles, 10.8 (3.5-20.2), 12.1 (5.6-26.4), and 12.7 (4.8-25.4); E, by Δheight SDS 1-6y tertiles, 10.8 (5.0-20.2), 12.4 (3.9-23.7), and 11.9 (4.5-24.8); F, by Δweight-for-height SDS 1-6y tertiles, 7.6 (2.9-18.3), 15.9 (6.8-33.5), and 12.4 (6.0-20.2). Conversion multiplier to SI units: DHEAS, µmol/l = µg/dL × 0.0271.

Table 1. Clinical and biochemical characteristics of the 78 children in the study

	All, n = 78	Girls, n = 43	Boys, n = 35	P^a
At birth				
Gestational age, wks	40.4 (36.6; 42.1)	40.3 (36.6; 42.0)	40.7 (36.9; 42.1)	.075
Length, cm	50.3 (1.8)	49.6 (1.5)	51.1 (1.7)	**< .001**
Length SD score	0.0 (0.9)	–0.3 (0.8)	0.3 (0.9)	**.003**
Weight, g	3650 (450)	3520 (450)	3800 (410)	**.006**
Weight SD score	0.1 (1.0)	0.0 (1.0)	0.2 (0.9)	.249
Weight-for-length, %	104.2 (7.7)	104.0 (6.9)	104.4 (8.6)	.819
Weight-for-length SD score	0.4 (0.9)	0.4 (0.8)	0.5 (1.0)	.888
At age 1 y				
Age, y	1.0 (0.9; 1.1)	1.0 (0.9; 1.1)	1.0 (0.9; 1.1)	.365
Length, cm	75.7 (2.5)	75.0 (1.9)	76.6 (1.9)	**.009**
Length SD score	–0.4 (1.1)	-0.4 (0.9)	–0.3 (1.2)	.931
ΔLength SD score 0 to 1 y	–0.3 (1.0)	-0.1 (1.0)	–0.6 (1.1)	**.024**
Weight, kg	9.8 (1.1)	9.4 (0.9)	10.3 (1.1)	**< .001**
Weight-for-length, %	100.1 (7.8)	98.8 (8.0)	101.5 (7.3)	.132
Weight-for-length SD score	–0.1 (1.0)	–0.2 (1.0)	0.1 (0.9)	.152
ΔWeight-for-length SD score 0 to 1 y	–0.5 (1.1)	–0.6 (1.1)	–0.3 (1.2)	.268
DHEAS, µg/dL	2.1 (0.4; 27.6)	2.2 (0.4; 22.7)	1.8 (0.4; 27.6)	.691
IGF-1, ng/mL	71.0 (32.3; 184.8)	77.4 (32.3; 136.4)	64.2 (35.7; 184.8)	.250
At age 6 y				
Age, y	6.1 (5.3; 6.3)	6.2 (5.7; 6.3)	6.1 (5.3; 6.3)	.630
Height, cm	117.3 (4.4)	116.7 (4.4)	118.0 (4.3)	.207
Height SD score	–0.3 (1.0)	–0.3 (1.0)	–0.3 (1.0)	.833
ΔHeight SD score 1 to 6 y	0.1 (0.7)	0.0 (0.8)	0.1 (0.7)	.883
Weight, kg	22.0 (16.7; 44.0)	21.0 (16.7; 30.5)	22.0 (18.2; 44.0)	.070
Weight-for-height, %	99.6 (84.5; 174.3)	98.8 (84.5; 127.4)	99.8 (88.7; 174.3)	.111
Weight-for-height SD score	0.1 (1.0)	-0.1 (1.0)	0.3 (1.1)	.088
ΔWeight-for-height SD score 1 to 6 y	0.1 (1.1)	0.1 (1.1)	0.2 (1.0)	.717
Waist circumference, cm	54.3 (47.0; 82.5)	53.5 (47.0; 68.5)	55.5 (50.0; 82.5)	**.034**
Waist-to-height ratio	0.47 (0.40; 0.65)	0.46 (0.40; 0.56)	0.47 (0.42; 0.65)	.140
DHEAS, µg/dL	12.1 (0.6; 76.1)	12.6 (0.7; 61.5)	9.1 (0.6; 76.1)	.224
IGF-1, ng/mL	183.2 (55.8; 355.6)	194.6 (55.8; 355.6)	159.8 (73.6; 264.8)	**.001**
Biochemical adrenarche[b], n (%)	8 (10.3)	4 (9.3)	4 (11.4)	.758
Clinical adrenarche[c], n (%)	6 (7.7)	5 (11.6)	1 (2.9)	.148

Continuous parameters with normal distribution are expressed as mean (SD), and those with nonnormal distribution as median (range). Bold values denote significant *P* values at the *P* less than .05 level. Conversion multipliers to SI units: DHEAS, µmol/l = µg/dL × 0.0271; IGF-1, nmol/l = ng/mL × 0.131.

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; IGF-1, insulin-like growth factor 1.

[a]Differences between sexes, analyzed using either the independent samples t test (normally distributed continuous variables), the Mann-Whitney U test (nonnormally distributed continuous variables), or χ^2 test (categorical variables).

[b]Defined as serum DHEAS concentration ≥ 40 µg/dL.

[c]Adult-type body odor in 3 girls, greasy hair in 2 girls and 1 boy. Acne, comedones, or pubic/axillary hair were not detected in any children.

36 weeks). Two girls and 1 boy had been born large for gestational age (birth length or weight > 2 SD score), whereas none of the children had been born small for gestational age. When compared with girls, boys had higher mean length and weight at birth and at age 1 year, and lower median serum IGF-1 concentration at age 6 year. When these anthropometric measures were analyzed as standardized SD scores, only the difference in birth length between the 2 sexes remained significant.

A. Associations With Serum DHEAS Concentrations

There was a strong positive correlation between serum DHEAS concentration at ages 1 and 6 years (r = 0.591, $P < .01$), and children in the highest DHEAS tertile at age 1 year had the highest DHEAS concentrations at age 6 years (Fig. 1A).

Serum DHEAS concentration at age 6 years correlated negatively with birth length SD score (r = –0.291, $P < .01$) and positively with first year Δlength SD score (r = 0.271, $P < .05$), and children in the lowest birth length tertile (Fig. 2A) and highest Δlength by age 1 year tertile (Fig. 2C) had the highest DHEAS concentrations at age 6 years. Birth size or growth measures by age 1 year did not associate with serum DHEAS concentrations at age 1 year. Neither birth weight, growth in weight-for-length by age 1 year, nor growth measures between the ages of 1 and 6 years had any significant associations with DHEAS concentrations at age 6 years (Fig. 2B, 2D, 2E, and 2F).

We found that serum DHEAS concentrations at age 6 years correlated positively with serum IGF-1 concentrations at age 1 (r = 0.289, $P < .05$) and 6 years (r = 0.291, $P < .01$), and that children in the highest IGF-1 tertile at age 1 year tended to have higher DHEAS concentrations at age 6 years (Fig. 1B).

B. Determinants for Higher DHEAS Levels at Age 6 Years

In age- and sex-adjusted logistic regression analyses, lower birth length, higher serum DHEAS concentration at age 1 year, and the change in length by age 1 year were determinants of falling into the highest DHEAS tertile at age 6 years (Table 2). In a mutually adjusted stepwise regression model including age, sex, birth size, growth measures, and biochemical covariates at age 1 year, only higher DHEAS concentration at age 1 year was an independent predictor of falling into the highest DHEAS tertile at age 6 years (Table 2).

C. Associations with Serum IGF-1 Concentrations

Children in the highest IGF-1 tertile at age 1 year had the highest IGF-1 concentrations at age 6 years (median [interquartile range; IQR]; 145.3 ng/mL [124.1-187.2], 187.7 [160.1-222.5], 205.6 [148.4-238.6]; $P = .005$). Growth in weight-for-height (141.9 ng/mL [119.4-197.3], 187.3 [160.2-203.8], 197.9 [146.8-238.1]; $P = .026$) but not in height ($P = .263$) from ages 1 to 6 years associated with serum IGF-1 concentrations at age 6 years. Advanced early growth in length by age 1 year associated with higher IGF-1 concentrations at age 1 year (62.3 ng/mL [49.4-84.1], 69.1 [53.3-81.3], 86.5 [61.4-93.1]; $P = .023$), but we did not find significant associations between birth size or growth in weight-for-length by age 1 year with IGF-1 concentrations at age 1 year.

Table 2. Probability of falling into the highest dehydroepiandrosterone sulfate tertile at age 6 years by birth size, growth measures, and biochemical covariates at age 1 year

	Age- and Sex-Adjusted Analyses		Mutually Adjusted Model[a]			
	OR (95% CI)	*P*	OR (95% CI)	*P*	R^2 (Model)	*P* (Model)
Birth length SD score	0.43 (0.23 to 0.80)	**.008**			0.422	**.001**
Birth weight SD score	0.64 (0.38 to 1.10)	.105				
ΔLength SD score 0 to 1 y	1.83 (1.09 to 3.08)	**.022**				
ΔWeight-for-length SD score 0 to 1 y	1.01 (0.63 to 1.63)	.956				
ΔHeight SD score 1–6 y	1.06 (0.50 to 2.22)	.887				
ΔWeight-for-height SD score 1 to 6 y	1.02 (0.64 to 1.64)	.927				
DHEAS SD score at age 1 y	2.71 (1.51 to 4.85)	**.001**	5.42 (1.54 to 19.1)	**.009**		
IGF-1 SD score at age 1 y	1.54 (0.94 to 2.53)	.088				

Logistic regression models. Dichotomic dependent variable: highest serum DHEAS tertile at age 6 years (yes or no). Bold values denote significant *P* values at the *P* less than .05 level.

Abbreviations: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; IGF-1, insulin-like growth factor 1; OR, odds ratio.

[a]Mutually adjusted stepwise regression model including age, sex, and all variables in table.

4. Discussion

In this longitudinal study, we evaluated the trajectories of DHEAS and IGF-1 from ages 1 to 6 years and the associations of birth size and early growth with serum DHEAS concentrations at age 6 years in mostly term and appropriate for 78 gestational age–born Finnish children. We observed that children in the highest DHEAS concentrations at age 1 year had the highest DHEAS concentrations at age 6 years. Furthermore, lower birth length and increment in linear growth during infancy (0-1 years) were associated with higher serum DHEAS concentrations at age 6 years. Despite the fact that birth or infant growth measures did not have significant associations with DHEAS concentrations at age 1 year, increased first-year growth in length indicated higher IGF-1 concentrations already at age 1 year and, in turn, IGF-1 concentrations at age 1 year correlated with DHEAS concentrations at ages 1 and 6 years. Based on these results, we suggest that early factors, including prenatal stress and higher energy supply in early childhood, induce increased early linear growth and later weight gain, leading to IGF-1–modulated early maturation of adrenocortical zona reticularis and higher serum DHEAS concentrations by mid-childhood.

The most important and novel finding in our study was that higher serum DHEAS concentrations could be detected already at age 1 year in those children with the highest DHEAS levels later in mid-childhood. To the best of our knowledge, this has not been reported in previous studies. It has been reported that zona reticularis of the adrenal cortex becomes morphologically discernible at age 3 years [24] and that adrenal androgen secretion (measured by sensitive gas chromatography–mass spectrometry urine androgen metabolite analyses) increases gradually from around the same age [25]. However, children participating in the study by Remer et al [25] were older than 3 years and, based on our knowledge, measures of adrenal androgen secretion have not been reported in younger children. One may also think that higher serum DHEAS concentrations at age 1 year could reflect late regression of the fetal zone of the adrenal cortex. We cannot exclude this possibility in our study but, based on our knowledge, the fetal zone undergoes a rapid postnatal regression already in the first postnatal months [26].

The associations between birth size and early growth with later adrenal androgen secretion in childhood have been reported in several studies. In a large British birth cohort study of 770 children, lower birth weight and rapid postnatal weight gain by age 3 years were associated with higher adrenal androgen levels at age 8 years [4]. In another large cohort study of 972 Chilean children, increased weight gain from ages 2 to 4 years and later increment in height gain from ages 4 to 7 years were associated with higher serum DHEAS concentrations at age 7 years [6]. On the other hand, children with early maturation of the adrenal zona reticularis leading to premature adrenarche have had growth advancement and increased weight gain already in the first years of their lives [11, 12, 27]. Our results are well in line with these findings from previous reports, except we failed to find a significant association between birth weight or infant weight gain and childhood serum DHEAS or IGF-1 concentrations. However, there was a tendency toward an association of lower birth weight and higher weight gain by age 1 year with higher DHEAS levels at age 6 years. It is possible that the association of early growth advancement and earlier maturation of the adrenal zona reticularis is related to nutrition. In addition to the studies showing the association between early weight gain and DHEAS levels [4, 6], there are other reports suggesting the effect of increased energy supply and nutritional status on childhood adrenal androgen secretion. Childhood body mass index correlated with higher childhood adrenal androgen secretion [28], and early adiposity rebound was associated with obesity [29] and premature adrenarche [12]. Also, fat mass and animal protein intake in childhood were positively associated with adrenal androgen secretion in one German study of 137 prepubertal children ages 3 to 12 years [8].

IGF-1 may be a key modulator in a process in which early growth advancement is associated with an earlier increase in adrenal androgen secretion. The inverse relationship of IGF-1 with birth size [10, 30-32] and the positive association of IGF-1 with childhood

growth rate and current body size [10, 30, 32, 33] have been reported in several studies. In one of these studies, 50 children born small for gestational age had early catch-up growth and increased IGF-1 levels by age 3 years [30]. Similarly, lower birth weight, postnatal catch-up growth, and rate of weight gain by age 2 years were associated with higher IGF-1 levels by age 5 years in a British cohort of 497 children [10]. On the other hand, children with premature adrenarche tend to have higher circulating IGF-1 levels than their normally developing peers [11, 13, 34, 35]. Our findings are well in line with these previous studies because increased growth in length by age 1 year and later increased weight gain by age 6 years were associated with higher IGF-1 levels at age 1 and 6 years, respectively. In addition to regulating human growth [36], IGF-1 may promote adrenal maturation and adrenal androgen secretion [37-39], and thus could be a link between postnatal growth rate and later childhood adrenal androgen secretion.

A major strength of our study is its prospective design. Limitations include the relatively small sample size; some associations, especially those between low birth weight or rapid early weight gain and later serum DHEAS concentrations, might have been significant in a larger cohort. The lack of associations between serum DHEAS concentrations and body weight changes could also be explained by metabolic and nutritional status affecting metabolic clearance rates of DHEAS and its binding proteins [40]. Regarding the prevalence of clinical and biochemical adrenarche in girls and boys, our findings in this cohort showed a similar pattern to that reported in another Finnish cohort [41]. Because the clinical presentation of adrenarche is sexually dimorphic [41], it might have been appropriate to analyze the sexes separately, which was not possible because of the small sample size. Because we did not have appropriate parental data, we were also unable to control the analyses with maternal or paternal developmental patterns. It should also be noted that only DHEAS but no other androgen precursors or active androgens were measured in this study.

In conclusion, higher circulating DHEAS and IGF-1 concentrations already at age 1 year indicate higher DHEAS concentration at age 6 years. Moreover, lower birth length and early advancement in linear growth are associated with higher serum DHEAS concentrations at age 6 years. Similarly, early growth in length by age 1 year indicates higher IGF-1 levels at age 1 year, and increased weight gain from ages 1 to 6 years is associated with higher IGF-1 levels at age 6 years. Our findings suggest that part of adrenarchal programming already takes place by the end of infancy and that IGF-1 may be one of the modulators in this process. However, this preliminary hypothesis of an early programming of adrenarche needs to be confirmed in a larger cohort using a highly sensitive steroid panel.

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