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ORIGINAL RESEARCH

A Twin-Sibling Study on Early Growth and Hormone Levels in Adolescents

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Abstract This study addresses how growth during sensitive developmental periods and genes may affect hormone levels in late adolescence. We analyzed hormone levels of dehydroepiandrosterone sulfate (DHEAS) and insulin-like growth factor-I (IGF-I), which are hypothesized to be two pathways linking early growth with adult diseases (such as type 2 diabetes and cardiovascular disease) via their effects on enhanced insulin resistance. In a twin-sibling study, we tested whether there is an association between reduced intra-uterine growth and higher DHEAS or IGF-I levels in serum during adolescence, and we examined the contribution of insulin to the link between early growth and higher DHEAS and/or IGF-I levels. Anthropometric and hormone data were collected in 18-year-old twins (184 pairs) and their non-twin siblings (n = 98). Neither birth weight nor current body size predicted serum DHEAS and IGF-I levels. In the subsample of children who showed catch-up growth in weight during infancy, the children of lower birth weight had significantly higher serum DHEAS and IGF-I levels, but these were not related to insulin levels. Variation in serum DHEAS, IGF-I and fasting insulin levels was largely explained by genetic factors (73, 78 and 61 % respectively). Thus, early growth affects hormone levels in adolescence, but only in children with catch-up growth after birth. No evidence was found that early growth enhances insulin resistance via the hormones DHEAS or IGF-I.

Keywords Twin-sibling design · DHEAS · IGF-I · Insulin · Heritability · Early growth

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Introduction

Optimal growth during sensitive developmental periods is of great importance for health in later life. Restricted intrauterine growth has been associated with numerous somatic conditions, such as type 2 diabetes and cardiovascular disease, and also with less favorable neurodevelopmental, psychosocial and behavioral outcomes (Saenger et al. 2007). It has been hypothesized that these links could result from programming of metabolic pathways with subsequent development of insulin resistance. Low birth weight has been associated with early and exaggerated adrenal androgen secretion before puberty (premature adrenarche). This is a condition that is related to several disease risk factors such as insulin resistance and dyslipidemia and in girls predicts later ovarian hyperandrogenism (Denburg et al. 2002; Ibanez et al. 1999, 2002). Therefore, increased adrenal androgen production might be one of the metabolic mechanisms contributing to the link between early growth and adult diseases. Following these observations, several studies have shown that lower birth weight is also related to higher levels of the androgen dehydroepiandrosterone sulfate (DHEAS) in children with normal timing of adrenarche. At first, this association was only reported in small for gestational age (SGA) children (Ibanez et al. 1999; Veening et al. 2004), but later the

inverse relationship between birth weight and DHEAS levels was also described throughout the range of normal birth weights (Ong et al. 2004a; Opdahl et al. 2008). The combination of low birth weight and rapid weight gain in early postnatal life predicts higher DHEAS levels in childhood (Ong et al. 2004a). However, it has to be noted that there are also studies that did not find an association between low birth weight and increased androgen levels (Boonstra et al. 2004; Hernández et al. 2006; Jaquet et al. 1999).

A second hormone investigated in this study is insulin-like growth factor-I (IGF-I), which has a major role in the regulation of human growth (D'Ercole 1996). In utero and during infancy, growth and IGF-I levels are closely related to nutrition and insulin secretion, but largely independent of growth hormone (GH). Later in childhood, growth is determined by GH secretion, but the GH/IGF-axis remains partly dependent on insulin and nutrition. Serum IGF-I levels have also been reported to be related to birth weight: children of lower birth weight have low IGF-I levels at birth, but higher IGF-I levels in childhood during catch-up growth and in adulthood (Fall et al. 1995; Giudice et al. 1995; Poole et al. 2011). The higher IGF-I levels may have contributed to catch-up growth and normal stature, but are also associated with insulin resistance (De Zegher et al. 2002; Iñiguez et al. 2006). The peripheral insulin resistance results in higher circulating insulin levels, which may cause increased IGF-I levels as well because of a direct stimulatory effect of insulin on liver IGF-I production (Bereket et al. 1995).

Early postnatal growth appears to play a critical role in the association between fetal growth and adult disease risks. Insulin sensitivity was reduced in children born SGA, especially in children with rapid postnatal weight gain (Soto et al. 2003; Veening et al. 2002). Furthermore, catch-up growth is associated with adult obesity (Monteiro and Victora 2005), hypertension (Huxley et al. 2000), coronary heart disease (Eriksson et al. 1999) and type 2 diabetes (Forsen et al. 2000). In a large birth cohort study children with lower birth weight and the highest postnatal weight gain had higher DHEAS and IGF-I levels than other children (Ong et al. 2002, 2004a).

Most studies investigating the association between early growth and DHEAS or IGF-I levels have been done in (pre)pubertal children. The results from studies relating birth weight to DHEAS or IGF-I levels in late adolescence and adulthood were not consistent (Beck Jensen et al. 2011; Jaquet et al. 1999; Poole et al. 2011; Ruder et al. 2011; Szathmári et al. 2001; Tworoger et al. 2006). Here, we investigate this association in late adolescence. In a Dutch sample of 18-year old twins and their siblings, we first tested whether there is an association between reduced intrauterine growth and higher serum DHEAS or IGF-I levels in late adolescence, and investigated the role of postnatal weight gain on these associations. Secondly, we examined whether higher DHEAS or IGF-I levels were related to higher insulin levels. A twin-sibling design was chosen, so that the heritability of serum DHEAS, IGF-I and insulin levels in this adolescent population could be estimated, and the importance of genetic and environmental factors underlying associations could be obtained.

Method

Participants

Participants were contacted via the Netherlands Twin Register (NTR), established by the Department of Biological Psychology at the VU University in Amsterdam, the Netherlands (Boomsma et al. 1992, 2006). The study sample is part of a longitudinal project on physical and mental development and comprises 184 families of 18-year-old twin pairs and their siblings (Bartels et al. 2002). The initial sample was composed of 368 twins (mean age 18.14 years, SD = 0.48) and 98 siblings aged 7–35 years (mean age 18.78 years, SD = 4.89). Three families participated with two twin pairs. There were six incomplete twin pairs (only one twin took part). Zygosity of the same-sex twins was established by DNA analyses (Van Beijsterveldt et al. 2013). The twin sample consisted of 32 MZM (monozygotic male), 34 DZM (dizygotic male), 44 MZF (monozygotic female), 38 DZF (dizygotic female) and 39 DOS (dizygotic opposite- sex) twin pairs.

Blood withdrawal was performed in 347 twins and 81 siblings. Data were excluded for several reasons: congenital anomalies (2 twins); severe growth retardation (1 sibling); pregnancy (2 siblings). The final sample consisted of 345 twins and 78 siblings. Serum IGF-I is known to increase during childhood until it reaches a peak in puberty (14.5 years of age in girls and 15.5 years in boys), after which average levels decrease to low adult values (Juul et al. 1994). Because of this age effect, we selected female subjects older than 14.5 years of age and boys older than 15.5 years for the IGF-I analyses (342 twins and 60 siblings). Glucose and insulin data of non-fasting subjects were excluded (44 twins and 9 siblings). The exact numbers of DHEAS, IGF-I, glucose and insulin samples can be found in Table 1.

This study was approved by the Central Committee on Research Involving Human Subjects (CCMO04.2228/YW/Po3.1664C). Written informed consent was obtained from all participants and also from all parents of underage participants.

Procedure and measures

Participants were invited to come to the VUMC outpatient clinic in the morning, where a venous blood sample was taken after overnight fasting (mean time 10.35 h). Serum samples were centrifuged (3,000 rpm) during 10 min at room temperature and stored at −20 °C until assay. Serum DHEAS was measured by solid phase competitive chemiluminescent enzyme immunoassay (IMMULITE 2500, Siemens, USA). Intra- and inter-assay coefficients of variation (CVs) were 7 and 9 %, respectively. Serum IGF-I was measured by immunometric assay (IMMULITE 2500, Siemens, USA). Intra- and inter-assay CVs were 5 and 5 %, respectively. Glucose and insulin concentrations were measured in heparin plasma (see for details: Willemsen et al. 2010). Glucose concentrations were assessed using the Vitros 250 Glucose assay (Johnson & Johnson, Rochester, USA). The intra-batch CV was lower than 2 % and the inter-batch CV was lower than 4 %. Insulin measurements were performed using the Immulite 1000 Insulin Method (Siemens Medical Solutions, Breda, NL). Intra- and inter-assay CVs were lower than 6.5 and 6 % respectively. The cross-reactivity with proinsulin was 8.5 % and the sensitivity was 2 μIU/ml.

Height (cm) was determined to the nearest 0.1 cm and weight (kg) to the nearest 0.05 kg using a stadiometer and an electronic scale (SECA, Hanover, Md) during the visit to the outpatient clinic. Stage of puberty of the subjects was assessed by the same physician according to the criteria of Tanner (Tanner 1981). Regarding pubic hair development: 1 subject was at stage P1; 4 subjects at P2; 2 subjects at P3; 17 at P4; 204 at P5; and 181 at P6 (data not available in 14 cases). For Tanner stage of breast or genital development: 4 subjects were at stage 2; 6 subjects at stage 3; 44 subjects at stage 4; and 344 subjects at stage 5 (data missing in 25 subjects). Information on birth weight and gestational age was collected by surveys sent to the mother at the time of registration with the NTR, shortly after birth of the twins. Weight data at age 2 were obtained from the report with growth data measured by the Dutch National Health Service's (NHS) or, if not available for twins, from questionnaires collected around the twins' second birthday. We selected the measurement between the age of 1.5 and 2.5 years closest to the age of 2.0 years.

Birth weight was converted to standard deviation scores (SDS) using Swedish reference standards, because Dutch SDS reference values for birth weight were unavailable (Niklasson et al. 1991). Weight data at age 2 were standardized dependent on sex and age using the Dutch reference growth charts for the general population from 1997 (Fredriks et al. 2000a). Postnatal weight gain was calculated as the SDS for weight at age 2 minus the SDS for weight at birth; a gain in weight SDS greater than 0.67 was considered as clinically significant catch-up growth (Ong et al. 2000). Body mass index (BMI) at age 18 years was calculated as weight (kg) divided by height (m) squared. SDS were calculated for height and BMI at age 18 years with the software package Growth analyzer (Growth Analyzer 3 Analyzer and 3 Application, 2004), using the Dutch reference growth charts for the general population from 1997 (Fredriks et al. 2000a, 2000b). BMI reference values were available up to the age of 21 years (unavailable for 23 siblings).

Statistical analyses

Descriptive statistics were calculated on untransformed data in SPSS for Windows (version 18.0, SPSS Inc.). All statistical analyses were performed on square root-transformed DHEAS and IGF-I concentrations and log-transformed insulin levels, because these transformations gave the best approximation to a normal distribution of the data. Tests were carried out using structural equation modeling in the software package Mx (Mx: Statistical modelling, 2006) because of the dependency among variables that is present in family data. First, we tested the effects of covariates to be accounted for in the genetic analyses. Based on literature we selected the following covariates. For all hormones, the effects of age and BMI SDS were tested (Corvalán et al. 2013; Ong et al. 2002). For DHEAS and IGF-I the effect of fasting state (yes/no), and for DHEAS the effect of pubic hair development was assessed (Tanner 1981). The effect of the interaction between age and pubic hair development on DHEAS was tested with a dummy variable (age * pubic hair development). For IGF-I, Tanner stage and height SDS were analyzed (D'Ercole 1996). Then, we tested for effects of zygosity, twin-sibling status and sex on the mean and variance of DHEAS, IGF-I and insulin levels, if twin-sibling covariances could be constrained to equal DZ covariances and whether covariances differed between males and females. Based on these results, twin and twin-sibling correlations were estimated for the five zygosity groups (MZM-DZM-MZF-DZF-DOS). The twin-sibling correlation was constrained to equal the DZ correlation. The variation in DHEAS, IGF-I and insulin was decomposed into sources of additive genetic variance (A), non-additive genetic variance (D) or common environmental variance, and unique environmental variance (E). We tested for the significance of D, C and of A and D or C by dropping the components from the model. Submodels were compared to the full ADE or ACE model using the likelihood ratio test. Based on the twin and twin-sibling correlations model fitting started with an ADE model for DHEAS and IGF-I, and an ACE model for insulin.

To study the association between birth weight SDS and hormone levels (DHEAS/IGF-I/insulin), cross-trait correlations (between two variables within a subject) and cross-twin/sibling-cross-trait correlations (between a variable of one twin and another variable of the co-twin/sibling) were analyzed. We tested whether the cross-twin/sibling-cross-trait correlations differed between the MZ and DZ zygosity groups. To study the effect of catch-up growth (change in weight SDS 0–2 years greater than 0.67) on the association between birth weight SDS and hormone levels, we estimated the cross-trait correlations and cross-twin/sibling-cross-trait correlations in a subsample of 146 twins and 11 siblings who showed catch-up growth. To investigate whether insulin levels are related to DHEAS or IGF-I levels, cross-trait correlations and cross-twin/sibling-cross-trait correlations were calculated in the entire sample and in the subsample with catch-up growth. Linear regression analysis was conducted to analyze whether birth weight and current body size influenced hormone levels (DHEAS/IGF-I/insulin). This was tested by mixed-model analyses of variance in SPSS for Windows (version 18.0, SPSS Inc.) with sex, age, pubic hair development (DHEAS), birth weight SDS, BMI SDS (DHEAS, insulin), height SDS (IGF-I) as fixed factors and with family as a random factor to account for the within-family dependence of the dependent variable (DHEAS, IGF-I or insulin levels).A significance level of 0.05 was adopted for all analyses.

Results

Table 1 summarizes the data on birth weight SDS, change in weight SDS between birth and 2 years, current body size and hormone levels of twins and siblings by sex. DHEAS levels (μmol/L) were significantly associated with pubic hair development ($\beta = -0.05$; $\chi^2_1 = 40.29$, $p < 0.05$). There was a significant effect of the interaction between age and pubic hair development on mean DHEAS levels ($\beta = 0.02$; $\chi^2_1 = 36.23$, $p < 0.05$). IGF-I levels (nmol/L) were significantly associated with age (years) ($\beta = -0.19$; $p < 0.05$). In all subsequent analyses we allowed for these significant covariates. Subjects who did not fast were also included in the DHEAS and IGF-I analyses, as there were no differences in DHEAS and IGF-I levels between fasting and non-fasting subjects. None of the covariates influenced insulin levels significantly.

Zygosity did not affect the mean levels of DHEAS, IGF-I and insulin. There was a significant effect of sex on mean DHEAS, with males having higher DHEAS levels than females ($\chi^2_4 = 17.25$, $p < 0.05$). No significant sex difference in mean IGF-I was found. Males had significantly lower insulin levels than females ($\chi^2_4 = 16.95$, $p < 0.05$). The variance of DHEAS did not differ between males and females, while the variance of IGF-I was larger in females than in males ($\chi^2 = 10.79$, $p < 0.05$). The variance of insulin was larger in males than in females ($\chi^2 = 18.29$, $p < 0.05$). Mean DHEAS and IGF-I levels were

Table 1 Observed means of twins (first-born/second-born) and siblings by sex

	Twins				Siblings			
	Males		Females		Males		Females	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Birth weight SDS	82	−0.88 (0.97)	91	−0.84 (0.99)	32	0.15 (1.01)	40	0.12 (0.93)
	78	−0.91 (1.13)	92	−0.90 (1.12)				
Change in weight SDS 0–2 years	67	0.77 (1.17)	81	0.71 (0.90)	22	−0.19 (0.89)	28	0.07 (0.87)
	68	0.48 (1.18)	79	0.69 (1.04)				
Age (years)	82	18.14 (0.38)	92	18.20 (0.32)	36	18.67 (4.19)	42	19.39 (4.67)
	79	18.10 (0.69)	92	18.17 (0.21)				
Current height SDS	82	−0.12 (1.09)	92	0.14 (0.94)	36	−0.20 (0.97)	42	0.11 (0.87)
	79	−0.02 (0.96)	92	−0.03 (0.94)				
Current BMI SDS	82	0.07 (1.04)	91	0.13 (1.10)	26	0.27 (1.29)	29	0.39 (0.99)
	79	0.01 (1.10)	92	0.10 (1.03)				
DHEAS (μmol/L)	82	7.62 (2.72)	92	5.90 (2.93)	36	5.67 (2.89)	42	4.70 (2.24)
	79	8.32 (3.18)	92	5.45 (2.69)				
IGF-I (nmol/L)	81	36.86 (9.21)	92	35.75 (8.70)	24	34.38 (9.89)	36	32.94 (13.71)
	77	36.53 (9.49)	92	35.07 (8.59)				
Glucose (mg/dL)	73	97.27 (9.06)	82	91.60 (8.13)	30	95.52 (9.12)	39	94.06 (6.53)
	63	98.34 (8.78)	83	91.37 (8.88)				
Insulin (μU/mL)	72	7.63 (3.56)	83	9.56 (3.72)	30	7.89 (3.48)	39	10.25 (4.74)
	63	8.44 (4.31)	82	9.03 (3.32)				

SDS standard deviation score

Table 2 Twin and twin-sibling correlations for serum DHEAS, IGF-I and insulin levels with 95 % confidence intervals between brackets

	DHEAS	IGF-I	Insulin
MZ males	0.64 (0.41–0.78)	0.83 (0.70–0.90)	0.67 (0.42–0.80)
DZ/sibling males	0.31 (0.04–0.53)	0.43 (0.18–0.61)	0.52 (0.25–0.70)
MZ females	0.81 (0.68–0.88)	0.77 (0.60–0.86)	0.48 (0.20–0.67)
DZ/sibling females	0.33 (0.11–0.51)	0.10 (−0.12–0.34)	0.37 (0.12–0.56)
DOS/sibling males-females	0.34 (0.11–0.51)	0.00 (−0.24–0.24)	−0.13 (−0.35–0.12)

MZ monozygotic, *DZ* dizygotic, *DOS* dizygotic opposite sex

significantly higher in twins than in siblings ($\chi^2 = 12.88$, $p < 0.05$ and $\chi^2 = 10.14$, $p < 0.05$ respectively). The variance of DHEAS was similar in twins and siblings, while the variance of IGF-I and insulin was larger in siblings than in twins ($\chi^2 = 10.89$, $p < 0.05$ and $\chi^2 = 12.63$, $p < 0.05$ respectively). Constraining the twin-sibling covariance to equal the DZ covariance did not worsen the fit of the models of DHEAS, IGF-I and insulin. No sex effect was found on the covariance of DHEAS and IGF-I and insulin.

The twin and twin-sibling correlations for the five zygosity groups, presented in Table 2, suggest a large influence of genetic factors on DHEAS, IGF-I and insulin. The fact that the MZ correlations are more than twice the DZ-sibling correlations demonstrates influences of non-additive genetic factors on DHEAS and IGF-I. The correlations for insulin indicate influences of shared environment as well, because the MZ correlations are less than twice the DZ-sibling correlations. The similarity in same sex and opposite sex twin-sibling correlations in DHEAS indicates influences of the same underlying set of genes for males and females, while the opposite sex twin-sibling correlations for IGF-I and insulin are lower than the DZ twin-sibling correlations. Therefore, a model with sex limitation was used for IGF-I and insulin.

Table 3 gives the results for the genetic modelling and the standardized variance component estimates with the 95 % confidence intervals. The AE model fitted the DHEAS data best. Constraining additive and non-additive genetic factors at zero caused a significant worsening of fit, indicating significant genetic influences on DHEAS. Additive genetic effects explained 73 % of the variation in DHEAS. For IGF-I, dropping the D component from the full ADE model did not result in a deterioration of the model fit, while dropping both additive and non-additive genetic factors caused a significant loss of fit. Most variation in IGF-I (78 %) was explained by additive genetic factors. For insulin, we fitted a model in which the genetic correlation between boys and girls was constrained at zero, as the correlation in DOS pairs was zero. In this model, dropping A influences caused a significant loss of fit. Additive genetic factors accounted for 61 % of the variance.

The cross-trait correlations and cross-twin/sibling-cross-trait correlations between DHEAS/IGF-I/insulin and birth weight SDS were not significantly different from zero. The cross-trait correlation between birth weight SDS and DHEAS was $r = -0.05$ (CI −0.16 to 0.06); between birth weight SDS and IGF-I $r = -0.02$ (CI −0.13 to 0.09); and between birth weight SDS and insulin $r = -0.03$ (CI −0.14 to 0.08). The cross-trait correlations and cross-twin/sibling-cross-trait correlations between DHEAS/IGF-I and insulin were approximately zero, both in the entire sample and in the smaller sample with catch-up growth. So no association was found between DHEAS and insulin, or between IGF-I and insulin levels.

Table 4 provides the descriptive statistics of the catch-up growth sample. Figures 1 and 2 show that, within the group of catch-up growth, the subjects of low birth weight (lowest birth weight tertile) had the highest mean DHEAS and IGF-I levels. Both figures represent data from the twins and siblings with catch-up growth, the figures show similar trends when analysing data from twins and siblings separately. In regression analysis (Table 5), birth weight did not affect hormone levels significantly. However, in children who showed catch-up growth, birth weight SDS predicted DHEAS and IGF-I levels minimally, but significantly (DHEAS, $p < 0.01$; IGF-I, $p = 0.03$; Table 5). For every increase in birth weight SDS of 1.0, the square root-transformed DHEAS level decreased 0.10 μmol/l and the square root-transformed IGF-I level decreased 0.14 nmol/l. Regarding body size, BMI SDS predicted insulin levels significantly in the entire sample ($\beta = 0.04$; $p < 0.01$), and height SDS affected IGF-I levels significantly in the catch-up growth sample ($\beta = 0.16$, $p = 0.04$; Table 5).

Discussion

Twins had small but significantly higher mean serum DHEAS and IGF-I levels than their siblings. We hypothesized that this may be due to their smaller size at birth and subsequent catch-up growth. Twins are born with a significantly lower birth weight, but attain normal final height and weight compared to singletons (Estourgie-van Burk

Table 3 Genetic model fitting results for dehydroepiandrosterone sulphate (DHEAS), insulin-like growth factor-I (IGF-I) and insulin and standardized estimates of variance components for DHEAS, IGF-I and insulin with 95 % confidence intervals between brackets

	−2LL	df	χ^2	Δdf	c.t.m.	p	AIC
DHEAS							
1. ADE	540.59	412					
2. AE	540.90	413	0.31	1	1	0.58	−1.69
3. E	614.24	414	73.65	2	1	<0.01	69.65
IGF-I							
1. ADE males	831.93	393					
ADE females							
2. AE males	837.68	395	5.75	2	1	0.06	1.75
AE females							
3. AE[a]	836.06	395	4.13	2	1	0.13	0.13
4. E	899.08	397	67.15	4	1	<0.01	59.15
Insulin							
1. ACE males	3,164.65	355					
ACE females							
2. AE males	3,165.57	357	0.92	2	1	0.63	−3.08
AE females							
3. AE[a]	3,170.30	357	5.64	2	1	0.06	1.64
4. CE	3,188.39	357	23.73	2	1	<0.01	19.73

Standardized variance components

	V_A	V_D	V_C	V_E
DHEAS	0.73 (0.61–81)	–	–	0.27 (0.19–0.39)
IGF-I	0.78 (0.66–0.85)	–	–	0.22 (0.15–0.34)
Insulin	0.61 (0.47–0.71)	–	–	0.39 (0.29–0.53)

−2LL −2 log likelihood, *df* degrees of freedom, χ^2 Chi square statistic, *Δdf* difference in df, *c.t.m.* compared to model, *p* probability-value, *AIC* Akaike's information criterion, *A* additive genetic influences, *d* non-additive genetic influences, *C* common environment, *E* unique environment, V_A variance explained by additive genetic factors, V_D variance explained by non-additive genetic factors, V_C variance explained by common environment, V_E variance explained by unique environment

[a] No sex differences in variance component estimates (sex differences in means allowed)

Table 4 Descriptive statistics for twins and siblings with catch-up growth compared to the twins and siblings without catch-up growth (data on catch-up growth unavailable for 78 subjects)

	Catch-up growth		No catch-up growth	
	N	Mean (SD)	N	Mean (SD)
Twins	146 (93 %)		149 (79 %)	
Siblings	11 (7 %)		39 (21 %)	
Male sex	71 (45 %)		86 (46 %)	
Zygosity MZ/DZ	63 (43 %)/83 (57 %)		59 (40 %)/90 (60 %)	
Gestational age (weeks)[a]	157	37.95 (2.31)	188	36.97 (2.81)
Birth weight (kg)[a]	157	2.58 (0.49)	188	2.76 (0.69)
Birth weight SDS[a]	157	−1.26 (1.02)	188	−0.31 (0.91)
Change in weight SDS 0–2 years[a]	157	1.49 (0.70)	188	−0.22 (0.60)
Current height SDS	157	0.08 (0.94)	188	−0.07 (1.01)
Current BMI SDS[a]	154	0.22 (0.98)	181	−0.03 (1.11)

MZ monozygotic, *DZ* dizygotic, *SDS* standard deviation score

[a] Mean is significantly different between the two groups ($p < 0.05$)

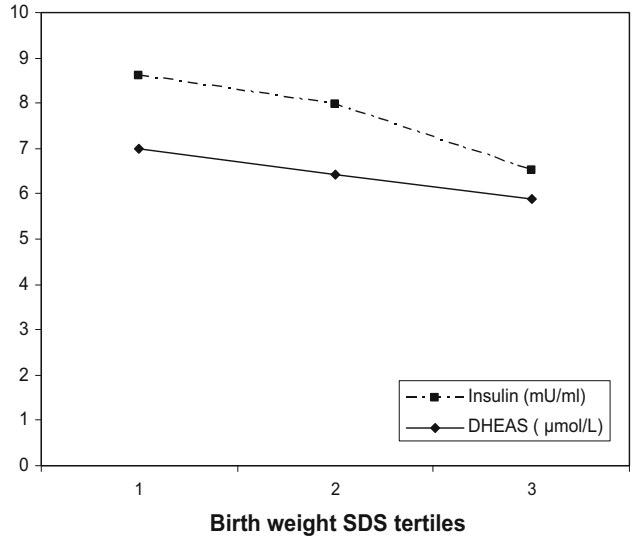

Fig. 1 Mean serum dehydroepiandrosterone sulfate and insulin levels in subjects with catch-up growth (n = 147) by tertiles of birth weight standard deviation score

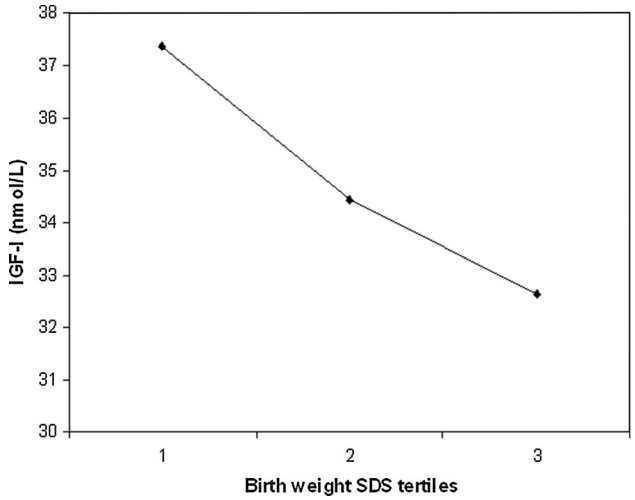

Fig. 2 Mean serum insulin-like growth factor-I levels in subjects with catch-up growth (n = 147) by tertiles of birth weight standard deviation score

et al. 2010). However, we found no relation between birth weight and adolescent hormone levels. Moreover, when we considered twins only (data not shown), we also found no relation between birth weight and adolescent hormone levels. When we looked at a subsample of children who showed catch-up growth, the children of lower birth weight had significantly higher DHEAS and IGF-I levels. Therefore, postnatal growth appears to be essential for the association between early growth and hormone levels in later life, which is in line with previous studies (Ong et al. 2002, 2004a; Beardsall et al. 2009). In a sample of 9-year-old twins (Beardsall et al. 2009), postnatal weight gain was associated with childhood risk factors for adult metabolic disease, such as blood pressure and insulin levels. It has to be noted that the higher DHEAS and IGF-I levels of the low birth weight children in the catch-up growth sample were all within the normal range and not of any clinical significance. From an epidemiological point of view, the trend of higher DHEAS and IGF-I levels in low birth weight children with catch-up growth is interesting.

To study whether DHEAS or IGF-I levels are related to insulin levels, we calculated the bivariate correlations between insulin and DHEAS or IGF-I. No association was found between DHEAS and insulin, or between IGF-I and insulin levels. Performing the analyses in the subsample with catch-up growth did not change these results. Therefore, our data do not support the hypothesis that DHEAS and IGF-I play a role in the association between early growth and adult metabolic disease by enhancing insulin resistance. Several other studies in adult twins and young women did not show a relation between DHEAS and insulin levels either (Jaquet et al. 1999; Nestler et al. 2002). However, the evidence is quite extensive that early androgen excess in children with premature adrenarche or adolescents with polycystic ovary syndrome is a significant risk factor for the development of the metabolic syndrome (Idkowiak et al. 2011). Moreover, experimental studies suggest that increased androgen levels are related to central fat deposition and reduced insulin sensitivity (Elbers et al. 1999; Ibanez et al. 2003; Nilsson et al. 1998). The fact that

Table 5 Regression coefficients between serum dehydroepiandrosterone sulfate, insulin-like growth factor-I or insulin levels and standard deviation scores for birth weight and current body size

	DHEAS[a]		IGF-I[b]		Insulin[b]	
	All	CUG	All	CUG	All	CUG
Birth weight SDS	−0.03 (NS)	−0.10 ($p < 0.01$)	−0.02 (NS)	−0.14 ($p = 0.03$)	−0.002 (NS)	−0.02 (NS)
BMI SDS	0.03 (NS)	0.06 (NS)	–	–	0.04 ($p < 0.01$)	0.03 ($p = 0.04$)
Height SDS	–	–	0.07 (NS)	0.16 ($p = 0.04$)	–	–

CUG catch-up growth, *NS* not significant

[a] Adjusted for sex, age and pubic hair development

[b] Adjusted for sex and age

we did not find any association between IGF-I and insulin levels may be explained by the age of the sample. In childhood IGF-I is of major importance for the regulation of postnatal longitudinal growth and brain development, and IGF-I levels are related to insulin levels. In adulthood the relation is presumably more complex (Ohlsson et al. 2009). IGF-I is involved in a variety of physiological and pathological processes, such as the regulation of blood pressure and body composition, insulin sensitivity and peripheral vascular resistance. The complexity of the IGF-I mechanism is illustrated by the results of a large Swedish cohort study, which shows that both low and high IGF-I levels associate with increased risk of cardiovascular events in elderly men (Carlzon et al. 2014). In conclusion, DHEAS and IGF-I may contribute to the link between early growth and adult diseases, but the mechanism is not fully understood yet. Another possibility is that genetic effects play an important role in explaining the association between early growth and adult disease risks. For example, (Freathy et al. 2010) found a genetic association between lower birth weight and type-2 diabetes. Future studies may identify more genes underlying the association between early growth and disease risks in later life.

In this study we observed that subjects of the lowest birth weight tertile and highest current BMI tertile had significantly higher mean fasting insulin levels ($n = 30$, mean = 11.07 μU/mL, SD = 5.01) than subjects of high birth weight with low current BMI ($n = 39$, mean = 7.40 μU/mL, SD = 2.36). An increased insulin level is one of the first signs of the development of insulin resistance (Buse et al. 2008). The group of children with low birth weight and high current BMI is at risk for developing insulin resistance and should be warned and encouraged to lose weight. It is well-known that size at birth, rapid postnatal weight gain and current body size are important determinants of insulin resistance (Ong et al. 2004b; Whincup et al. 1997; Yarbrough et al. 1998). The evidence, showing that intrauterine growth restriction and rapid postnatal weight gain in infancy are associated with adverse conditions in later life, should result in more attention for growth of the fetus and infant. First, it is important to avoid intrauterine growth restriction which may have negative consequences itself, but it also predisposes to catch-up growth. In fact, most children who are born SGA experience catch-up growth (Saenger et al. 2007). In our sample the correlation between birth weight SDS and catch-up growth ($r = -0.58$; $p < 0.01$) is high and therefore it is hard to differentiate the effects of low birth weight from those of catch-up growth. Pregnancy of twins or higher-order multiples is a well-recognized risk factor for intrauterine growth restriction. Such pregnancies may constitute an undesirable complication of IVF and of ovulation induction. Therefore, efforts should be made to assure a singleton birth when treating infertility. Second, after birth balanced weight gain is of great importance. This insight becomes even more important by the recent warning of the Dutch NHS that Dutch babies have become fatter, have a higher caloric intake and less exercise than before (Smit 2014). These observations should result, for example, in information programs for (future) parents and health care workers pointing out the importance of balanced weight gain in infancy and childhood. Breast feeding should be recommended because breast feeding leads to lesser high weight gain in infancy and reduces obesity risk in later life by about 20 % compared to infant formula (Koletzko et al. 2013).

Our study population included twins and their siblings. Although intrauterine growth in twins may be different from that in singletons (Doyle et al. 1999), the associations of size at birth with cardiovascular risk factors is similar as it is in non-twins (Dwyer et al. 1999; IJzerman et al. 2000; Iliadou et al. 2004) and twin studies may help us in revealing the mechanisms underlying the association between early growth and disease in later life. Next to investigating the influence of early growth, this sample provided the unique opportunity to study the importance of genetic effects on the hormones of interest in adolescence. This is the first study to report heritability estimates of serum DHEAS, IGF-I and insulin levels in late adolescence. A significant contribution of genetic effects to serum DHEAS levels was found, explaining 73 % of the variation. The remaining proportion of the variance was accounted for by non-shared environmental influences. The fact that the within-pair correlations for dizygotic same-sex and opposite-sex pairs were similar suggested the same source of inter-individual variation in males and females. This is in line with the findings of a large Australian twin study (Nestler et al. 2002), which reported a heritability of about 60 % in adults. Individual differences in serum IGF-I levels were mainly controlled by genetic factors in late adolescence with a heritability of 78 %. This estimate is about as high as findings at birth (cord blood) and in childhood (Kao et al. 1994; Verhaeghe et al. 1996). A study in female pubertal twin pairs (age 11.45 ± 0.18 years) reported a heritability of 59, while 18 % of the variance could be attributed to age (Li et al. 2005). The proportion of variance explained by non-shared environmental effects was similar to ours (22 %). Hong et al. (1996) showed that genetic influences on the variation in IGF-I remain important in later life with a heritability estimate of 63 % in middle-aged and elderly twins. The non-significant correlation for IGF-I in opposite-sex pairs ($r = 0.00$; Table 2) in our study suggests a different source of inter-individual variation between males and females. We modelled this as by constraining the genetic correlation in DOS pairs at zero, but recognize that this explanation

needs to be explored in larger studies. Within sex, the estimate of heritability was 61 %, which is comparable to estimates reported previously in younger children (65 %) and higher than those in adults (20–41 %) (Beardsall et al. 2009; Nestler et al. 2002; Snieder et al. 1999).

In conclusion, early growth may affect hormone levels in adolescence, but only in the children with catch-up growth after birth. Therefore, postnatal growth appears to be essential for the association between birth weight and serum DHEAS and IGF-I levels in later life. No evidence was found to support the hypothesis that early growth is linked to disease in later life via the hormones DHEAS and IGF-I by enhancing insulin resistance. Genetic effects are strong in adolescence explaining most of the variation in serum DHEAS, IGF-I and insulin levels.

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Conflict of Interest G. Frederiek Estourgie-van Burk, Meike Bartels, Dorret I. Boomsma declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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