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ORIGINAL ARTICLE

Is a child's growth pattern early in life related to serum adipokines at the age of 10 years?

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BACKGROUND/OBJECTIVES: Growth parameters during infancy and early childhood might predict adipokine levels later in life. This study investigates the association between peak growth velocities, body mass index (BMI) and age at adiposity rebound (AR), with leptin and adiponectin levels at age 10 years.
SUBJECTS/METHODS: Peak height (PHV) and weight (PWV) velocities were calculated from height and weight measurements obtained between birth and age 2 years from 2880 children participating in the GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) and LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics) birth cohorts. BMI and age at AR were calculated using BMI measurements between age 1.5 and 12 years. Blood samples were collected during a physical examination at age 10. Adiponectin and leptin levels were measured by radioimmunoassay. Linear regression models were fitted after adjustment for potential confounding factors and results are presented per interquartile range increase in the exposure.
RESULTS: Age at AR was negatively associated with leptin in males and females (percent difference β^*: -41.71%; 95% confidence interval: (-44.34; -38.96) and β^*: -43.22%; (-45.59; -40.75), respectively). For both males and females PWV (β^*: 14.23%; (7.60; 21.26) and β^*: 18.54%; (10.76; 26.87), respectively) and BMI at AR (β^*: 63.08%; (55.04; 71.53) and β^*: 67.02%; (59.30; 75.10), respectively) were positively associated with leptin levels. PHV showed a positive effect on leptin in females only (β^*: 10.75%; (3.73; 18.25)). Growth parameters were not significantly associated with adiponectin except for age at AR among females (β: 0.75 ng/ml; (0.42; 1.09)) and PWV among males (β: 0.45 ng/ml; (0.11; 0.79)).
CONCLUSION: Growth patterns in early life may be associated with leptin levels at age 10 years.

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INTRODUCTION

Several studies in both children and adults have reported an association between weight gain during the first years of life and the prevalence of obesity later in life.[1–4] A few of these studies applied longitudinal models to derive growth parameters such as weight and height growth velocities in infancy[5–7] and the time of adiposity rebound (AR).[8–10] During childhood, one's body mass index (BMI) increases from birth up to the adiposity peak that occurs at ~8 to 9 months of age. After this time, one's BMI decreases until the point of AR, which typically occurs within the age range of 5–7 years. Usually, an early AR predicts a higher BMI later in life.[9,11] Obesity is also related to adipokines, such as leptin and adiponectin, which regulate appetite and food intake.[12,13] Leptin levels are elevated in obese subjects, whereas adiponectin concentrations tend to be lower.

Very few studies have investigated the relationship between birth weight and adipokine concentrations during adulthood.[14,15] A study of Swedish women found an inverse relationship between birth weight and leptin levels during adulthood.[15] Another study investigated the effect of weight gain during infancy on appetite regulatory hormones at age 17 and found high weight gain to be associated with ghrelin and adiponectin levels.[16] Whether different growth parameters derived from longitudinal models such as peak growth velocities as well as the time of the AR are associated with adipokine levels later in life has not yet been examined. Therefore, we aimed to investigate the association between different growth parameters and adipokine levels as well as BMI at the age of 10 years. We used data from a subsample population, originating from two German birth cohorts, for whom blood samples at the age of 10 years were available. To cover different periods of growth, especially sensitive periods in the first years of life for the development of overweight and other diseases later in life, we modelled height and weight velocities during the first 2 years of life as well as age and BMI at the time of AR.

MATERIALS AND METHODS

Study population

Data from two German birth cohorts of healthy full-term neonates with very similar study designs were combined for these analyses. GINIplus

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(German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) is an ongoing birth cohort study initiated to prospectively investigate the influence of a nutrition intervention during infancy on allergy development. Between September 1995 and July 1998, a total of 5991 newborns were recruited in Munich and Wesel. The cohort is composed of an intervention ($n = 2252$) and a non-intervention group ($n = 3739$), for which group assignment was based on family history of allergy. The intervention comprised of a randomised controlled trial to compare the effect of hydrolysed formula vs conventional cow's milk formula on the development of allergic diseases. Details of the study design have been described elsewhere.[17,18] LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics) is an ongoing population-based birth cohort study designed to assess the influence of lifestyle factors on immune system and allergy development. In total, 3097 healthy full-term neonates were recruited in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999. A detailed description of screening and recruitment has been described previously.[19,20]

All analyses in this study are based on a subsample of 2880 children; participation in the physical examination at the age of 10 and available leptin and/or adiponectin concentrations at the age of 10 were the inclusion criteria.

For both studies, approval by the respective local ethics committees (Bavarian Board of Physicians, University of Leipzig, Board of Physicians of North-Rhine-Westphalia) and written consent from all participating families were obtained.

Physical examination and laboratory analyses

Blood samples were collected from 2894 children (1088 and 1806 from the LISAplus and GINIplus studies, respectively) during the physical examination at 10 years of age; however, only data on 2880 children are available for this analysis. The blood was drawn during the day between 0700 and 2030 hours. Blood samples were centrifuged after collection and stored frozen at $-80\,^{\circ}C$ until assayed for leptin, adiponectin, estradiol (females) and testosterone (males). Leptin and adiponectin concentrations in serum were measured using a commercially available radioimmunoassay (Mediagnost, Reutlingen, Germany). The sensitivity of the test was 0.1 ng/ml and 0.6 μg/l for leptin and adiponectin, respectively. Intra- and interassay coefficients of variation were between 4.0 and 10.4% for leptin samples in the range of 2.1–38.1 ng/ml. The intra- and interassay coefficients of variation were between 2.35 and 8.59% for adiponectin samples ranging from 3.36 to 15.19 mg/l. Serum samples were measured for testosterone and estradiol by the fully mechanised immunoassay system Modular (Roche, Mannheim, Germany). The analytical sensitivity was 0.087 nmol/l for testosterone and 18.4 pmol/l for estradiol. Intra- and interassay coefficients of variation were below 4.06 and 2.83% for 6.2 and 20.2 nmol/l testosterone, respectively. For estradiol, intra- and interassay coefficients of variation were lower than 5.29 and 3.56% for 378 and 1941 pmol/l.

Definition of growth parameters and confounding variables

Weight and height measurements during infancy and childhood were obtained from 'baby books' created during preventive medical check-ups ('U-Untersuchungen') offered to all children in Germany. These physical examinations are conducted by a paediatrician at birth, days 3–10, weeks 4–6 and months 3–4, 6–7, 10–12, 21–24, 43–48 and 60–64. In this study, many of the children participated in the corresponding medical check-ups before or after the scheduled time period. In addition, weight and height measurements were recorded at the physical examination at the GINIplus and LISAplus 10-year follow-up (age range: 9–12 years).

Weight and height growth curves were calculated up to age 2 years according to the modified Reed1 model, as previously described.[7,21–23] Thereby, individual growth curves were computed separately for females and males using nonlinear random effects models. Peak weight velocity (PWV) and peak height velocity (PHV) were defined as the maximum of the first derivatives of the weight and height growth curves, respectively.

To determine the BMI and age at the AR, cubic models for age including random intercept and random slope components and adjustment for sex were fitted on the logarithm of BMI.[24] In addition, interaction terms between sex and linear as well as quadratic age terms were included in the model.[24] For fitting the model, age was restricted to the time period from 1.5 to 12 years and each child needed at least three available BMI measurements in this time interval to be included. For each subject, BMI and age at AR were defined using the point at which the minimum of each respective individual BMI curve occurred.

The set of confounders included gender, age at the physical examination, study centre (Munich, Leipzig, Wesel, Bad Honnef), maternal smoking during pregnancy, birth weight and whether the child was fasting at the time the blood sample was drawn. Furthermore, parental education levels were defined using the highest number of years of education achieved by either parent (low for less than 10 years, intermediate for 10 years and high for more than 10 years). Onset of puberty was defined based on measured oestrogen and testosterone levels at age 10 years and categorised as detectable (>18.4 pmol/l for estradiol and >0.09 nmol/l for testosterone) and non-detectable. Moreover, BMI at the physical examination at 10 years of age was used for stratification.

Statistical analyses

Multiple linear regression models were used to analyse the linear association between growth parameters and BMI at 10 years, leptin as well as adiponectin levels. In order to normalise the distribution of the outcome variables for the statistical analyses, leptin and BMI at 10 years were log transformed. The outcome variable adiponectin was already normally distributed. All models were adjusted for gender, study centre, age at physical examination, fasting status, onset of puberty, birth weight, parental education level and smoking during pregnancy.

In a separate analysis, models examining the association between growth parameters and adipokines were stratified by tertiles of BMI *z*-scores at the age of 10 years to investigate the impact of this variable on the results. For this additional analysis, BMI was transformed to age- and sex-specific s.d. scores (*z*-scores) according to the World Health Organisation (WHO) growth standards.[25]

All analyses were also stratified by sex, in which sex-specific BMI tertiles were calculated.

The results are presented as regression coefficients (β) for adiponectin and as percent differences in the dependent variable (β^*) for leptin and BMI at age 10, per interquartile range (IQR) increase in the exposure with corresponding 95% confidence intervals. *P*-values below 0.05 are used to indicate statistical significance. All analyses were performed using the statistical software package R, version 2.15.1.[26]

RESULTS

Study characteristics stratified for males and females as well as for the combined population are shown in Table 1. Half of the study population were males (51.04%) and 62.43% were children participating in the GINIplus study. The median of PWV and PHV was 1.05 kg per month (IQR = 0.29) and 3.65 cm per month (IQR = 0.55), respectively. In general, males had higher PWV and PHV than females (1.14 vs 0.95 kg/month and 3.76 vs 3.50 cm/month, respectively). The median age at AR was 5.86 (IQR = 1.51) years and the median BMI at AR was 15.10 (IQR = 1.32) kg/m^2. For the adipokines, females had higher leptin and adiponectin levels than males (median 3.61 vs 2.09 ng/ml and median 9.88 vs 9.53 ng/ml, respectively).

Table 2 presents the results for the association between growth parameters and BMI at 10 years of age for the total population and stratified for males and females. PHV and PWV and BMI at AR were positively and significantly associated with BMI at 10 years in the total population (β^*: 1.84–13.84%; *P*-value: <0.0001). A negative and statistically significant relationship was found between the age at AR and BMI at 10 years (β^*: -10.83%; *P*-value: <0.0001). Results were consistent for both males and females.

Results for the relationship between growth parameters and adipokines are summarised in Table 3. There was a significant negative association between age at AR and leptin levels (β^*: -41.71 and -43.22%; *P*-value: <0.0001, for males and females, respectively). BMI at AR and PWV was both positively significantly associated with leptin levels in the total population as well as in the sex-stratified populations. However, there was a substantial difference in the relationship between PHV and leptin concentrations across sexes (males: β^*: 2.33%; *P*-value: 0.4793 and females: β^*: 10.75%; *P*-value: 0.0023).

Table 1. Characteristics of the children who participated in the 10-year follow-up of the GINIplus and LISAplus studies (with adipokine data)

	Median (25th, 75th percentile) or % (n/N)					
	Male (n = 1470)		*Female (n = 1410)*		*Total (n = 2880)*	
Cohort						
LISAplus, %	39.39	(579/1470)	35.67	(503/1410)	37.57	(1082/2880)
GINIplus, %	60.61	(891/1470)	64.33	(907/1410)	62.43	(1798/2880)
Study centre						
Munich, %	55.24	(812/1470)	54.47	(768/1410)	54.86	(1580/2880)
Wesel, %	29.25	(430/1470)	30.85	(435/1410)	30.03	(865/2880)
Leipzig, %	10.34	(152/1470)	9.43	(133/1410)	9.90	(285/2880)
Bad Honnef, %	5.17	(76/1470)	5.25	(74/1410)	5.21	(150/2880)
Age, years	10.17	(10.08, 10.29)	10.18	(10.08, 10.31)	10.18	(10.08, 10.31)
Parental education[a]						
Low, %	6.19	(91/1469)	5.04	(71/1408)	5.63	(162/2877)
Medium, %	25.66	(377/1469)	26.28	(370/1408)	25.96	(747/2877)
High, %	68.14	(1001/1469)	68.68	(967/1408)	68.40	(1968/2877)
Smoking during pregnancy, %	11.96	(163/1363)	13.55	(174/1284)	12.73	(337/2647)
Birth weight, kg	3.54	(3.22, 3.84)	3.39	(3.10, 3.69)	3.46	(3.16, 3.76)
BMI at 10 years, kg/m^2	16.85	(15.69, 18.52)	16.87	(15.60, 18.79)	16.86	(15.64, 18.60)
Overweight at 10 years[b], %	22.32	(325/1456)	19.25	(268/1393)	20.81	(593/2849)
Age at AR, years	5.88	(5.06, 6.53)	5.83	(4.99, 6.53)	5.86	(5.02, 6.53)
BMI at AR, kg/m^2	15.13	(14.54, 15.86)	15.07	(14.44, 15.79)	15.10	(14.50, 15.82)
Peak weight velocity, kg/month	1.14	(1.02, 1.28)	0.95	(0.84, 1.08)	1.05	(0.91, 1.19)
Peak height velocity, cm/month	3.76	(3.53, 4.02)	3.50	(3.25, 3.77)	3.65	(3.38, 3.92)
Fasting at the time of sampling, %	16.12	(237/1470)	18.94	(267/1410)	17.50	(504/2880)
Puberty[c], %	26.88	(379/1410)	74.06	(1002/1353)	49.98	(1381/2763)
Adiponectin, ng/ml	9.53	(6.90, 12.31)	9.88	(7.37, 13.05)	9.66	(7.11, 12.65)
Leptin, ng/ml	2.09	(1.34, 3.93)	3.61	(2.18, 6.34)	2.77	(1.65, 5.16)

Abbreviations: AR, adiposity rebound; BMI, body mass index; GINIplus, German Infant Nutritional Intervention plus environmental and genetic influences on allergy development; LISAplus, Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics; WHO, World Health Organisation. [a]Low for less than 10, medium for 10 and high for more than 10 years of school. [b]Defined according to WHO: standardised deviation score of BMI $> +1$ s.d. [c]Detectable defined as estradiol levels >18.4 pmol/l and testosterone levels >0.09 nmol/l, respectively.

Table 2. Associations between growth parameters per IQR increase and log transformed BMI at 10 years of age

	Total[a,b,c]				*Male*[a,b]				*Female*[a,b]			
	n	β	*95% CI*	P-*value*	n	β	*95% CI*	P-*value*	n	β	*95% CI*	P-*value*
Age at AR	2306	−10.83	−11.23, −10.42	<0.0001	1185	−10.25	−10.84, −9.65	<0.0001	1121	−11.38	−11.93, −10.81	<0.0001
BMI at AR	2306	13.84	13.36, 14.33	<0.0001	1185	13.53	12.85, 14.22	<0.0001	1121	14.10	13.40, 14.79	<0.0001
PWV	2340	4.63	3.84, 5.42	<0.0001	1210	4.55	3.54, 5.57	<0.0001	1130	4.80	3.54, 6.08	<0.0001
PHV	2340	1.84	1.03, 2.64	<0.0001	1211	1.27	0.20, 2.35	0.0199	1129	2.40	1.20, 3.62	0.0001

Abbreviations: AR, adiposity rebound; BMI, body mass index; CI, confidence interval; IQR, interquartile range; PHV, peak height velocity; PWV, peak weight velocity. [a]Results presented as percent differences in the dependent variable. [b]Adjusted for study centre, age at physical examination, fasting status, onset of puberty, birth weight, parental education level and smoking during pregnancy. [c]Additionally adjusted for sex.

Age at AR and PWV had a significant effect on the adiponectin levels in the combined population (β: 0.43 and 0.41 ng/ml; *P*-value: 0.0003 and 0.0026, respectively). In the sex-stratified analyses, the effect of PWV was only significant among males. Age at AR was associated with adiponectin levels among females but not among males (β: 0.75 ng/ml; *P*-value: <0.0001 and β: 0.10 ng/ml; *P*-value: 0.5511, respectively).

We also tested the interaction between sex and growth parameters. The interaction term for age at the AR was significant for the association with BMI at 10 years of age as well as adiponectin levels, where the associations were stronger in females than in males.

Sensitivity analyses stratified by fasting status showed substantially the same relationship between growth parameters and adipokine concentrations (data not shown).

We also investigated the association between growth parameters and adiponectin and leptin levels stratified by tertiles of BMI *z*-scores at 10 years of age (Figures 1 and 2). Age at AR was significantly inversely associated with leptin concentrations in all BMI tertiles and the effect became stronger with increasing BMI (β* in the first BMI tertile: −12.04% for females and −9.96% for males vs β* in the third BMI tertile: −32.53% for females and −29.24% for males). For adiponectin, the positive relationship with age at AR was significant only in the second and third BMI tertiles among females (β: 0.96 and 0.92 ng/ml, respectively). BMI at AR showed a positive effect on leptin levels in the first and third BMI tertiles. A similar pattern was found for PWV and leptin in the total study population; however, the association was negative in the highest BMI category.

DISCUSSION

An early AR was associated with increased levels of leptin at 10 years of age in our study. Furthermore, BMI at AR and increased weight gain (PWV) during infancy were positively associated with leptin levels among both females and males. Similar results were

Table 3. Associations between growth parameters per IQR increase and adipokines

	Total[a,b]				Male[a]				Female[a]			
	n	*β*	*95% CI*	P-*value*	n	*β*	*95% CI*	P-*value*	n	*β*	*95% CI*	P-*value*
Adiponectin												
Age at AR	2311	0.43	0.20, 0.67	0.0003	1186	0.10	−0.23, 0.43	0.5511	1125	0.75	0.42, 1.09	<0.0001
BMI at AR	2311	−0.07	−0.32, 0.17	0.5504	1186	0.18	−0.16, 0.53	0.297	1125	−0.31	−0.66, 0.04	0.0794
PWV	2346	0.41	0.14, 0.67	0.0026	1211	0.45	0.11, 0.79	0.0102	1135	0.37	−0.05, 0.79	0.0868
PHV	2346	0.20	−0.07, 0.47	0.1436	1212	0.15	10.21, 0.52	0.4023	1134	0.28	−0.13, 0.68	0.1792
Leptin[c]												
Age at AR	2311	−42.65	−44.42, −40.82	<0.0001	1186	−41.71	−44.34, −38.96	<0.0001	1125	−43.22	−45.59, −40.75	<0.0001
BMI at AR	2311	65.43	59.80, 71.26	<0.0001	1186	63.08	55.04, 71.53	<0.0001	1125	67.02	59.30, 75.10	<0.0001
PWV	2346	15.84	10.77, 21.13	<0.0001	1211	14.23	7.60, 21.26	<0.0001	1135	18.54	10.76, 26.87	<0.0001
PHV	2346	6.37	1.61, 11.35	0.0082	1212	2.33	−4.00, 9.08	0.4793	1134	10.75	3.73, 18.25	0.0023

Abbreviations: AR, adiposity rebound; BMI, body mass index; CI, confidence interval; IQR, interquartile range; PHV, peak height velocity; PWV, peak weight velocity. [a]Adjusted for study centre, age at physical examination, fasting status, onset of puberty, birth weight, parental education level and smoking during pregnancy. [b]Additionally adjusted for sex. [c]Presented as percent differences in the dependent variable.

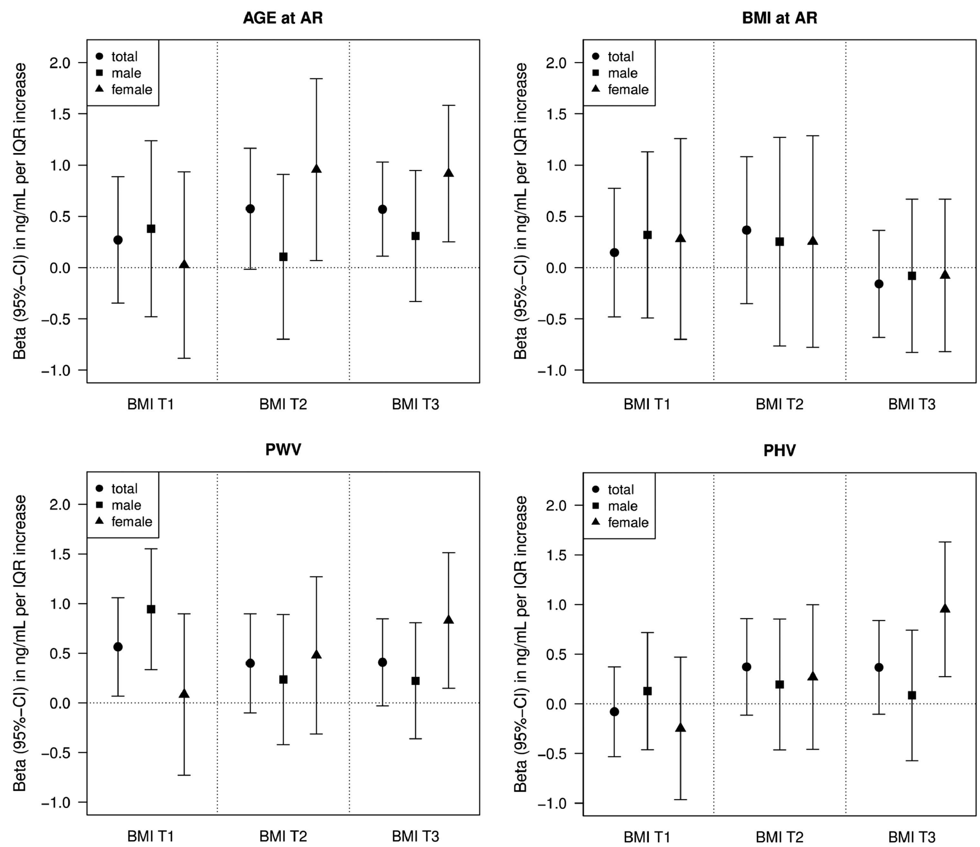

Figure 1. Associations between growth parameters per IQR increase and adiponectin levels stratified by tertiles of BMI *z*-scores at age 10 (BMI T1: BMI z-score below the first tertile; BMI T2: BMI z-score in the second tertile; BMI T3: BMI z-score above the third tertile).

found for the relationship between growth parameters and BMI at the age of 10. However, only PWV among males and the age at AR among females were positively and significantly associated with adiponectin.

There is only one previously published study on early weight gain and adipokines.[16] This study showed that weight gain from birth to 3 months of age and from birth to 9 months of age, defined as the difference between the age- and sex-specific s.d. scores for weight, were negatively associated with adiponectin and ghrelin levels at the age of 17, after correcting for body fat. However, the absolute adiponectin concentration was only associated with weight gain during the first 3 months of life. For leptin, no relationship was found with neither change in weight from birth to 3 months of age nor up to 9 months of age. A limitation of this study was its small sample size of only 95 children. By comparison, our study that includes ∼2000 children showed a positive association between PWV and adiponectin levels in males as well as in the total study population. Similar results were shown for the relationship of body size with adiponectin levels in 8-year-old boys in the ALSPAC study by Ong *et al*.:[27] BMI and body weight were positively associated with adiponectin among males but negatively associated among females.

The biological mechanisms explaining the association between weight gain during infancy and leptin and adiponectin concentrations later in life are unclear. However, it is already known that

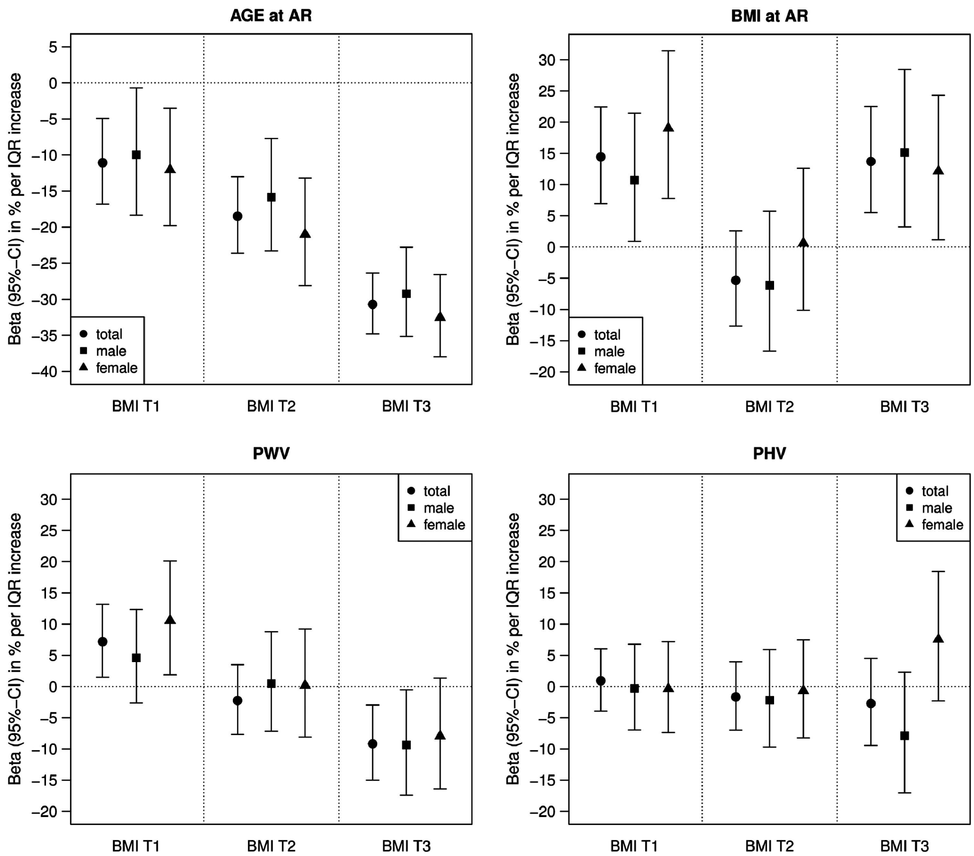

Figure 2. Associations between growth parameters per IQR increase and leptin levels stratified by tertiles of BMI *z*-scores at age 10 (BMI T1: BMI *z*-score below the first tertile; BMI T2: BMI *z*-score in the second tertile; BMI T3: BMI *z*-score above the third tertile).

the development of adipose tissue increases during infancy and the aptitude of adipocytes might also be influenced by nutrition.[28,29] Thus, leptin, which is secreted by adipocytes and is proportional to the mass of the adipose tissue,[30] might also be affected by weight gain patterns during infancy.

Other studies have investigated the association between birth weight and leptin and adiponectin levels during childhood or adolescence.[13,31,32] For instance, in the study of Giapros *et al.*,[13] higher adiponectin levels were found in children aged 6–8 years born 'large' for their respective gestational age compared with those born with a more average birth weight. Hence, adipokine levels may already be programmed in early life.

In contrast, cord leptin concentrations are negatively associated with postnatal catch-up growth. Thus, adipokine levels may already be determined *in utero* and may consequently regulate weight gain in infancy.[33] A mechanism by which intrauterine programming determines adiponectin secretion has also been suggested by some studies.[34,35]

In addition to these mechanisms, genetic determinants are likely to have a role in the regulation of early weight gain, thereby influencing adipokine levels later in life.[36]

In general, leptin levels are correlated with BMI and leptin concentrations are higher in females than in males, independent of BMI.[30,37] The relationship between growth parameters and leptin in our study was also stronger in females than in males. The secretion of leptin increases during childhood with the peak capacity occurring in puberty and adulthood.[38] As stated by Lecke *et al.*,[38] the concentrations of leptin and adiponectin change over time in females. Between the age of 5 and 8 years, leptin levels increase, whereas adiponectin levels decrease, independent of BMI. Adiponectin shows a negative association with percentage of body fat after this time period. This reversal of the relationship between adiponectin levels and BMI is more pronounced in older children.[38] Furthermore, adiponectin concentrations are inversely associated with pubertal and physical development.[39] These might be the reasons behind our finding of a positive association between PWV and adiponectin levels in males, as the children in our study were on average 10 years of age. Thus, only a few boys were already showing signs of puberty.

The major strengths of the current study are the longitudinal study design and the longitudinal growth modelling. Growth parameters were estimated from birth to 10 years of age at 10 time points. We are among the first to calculate different growth parameters for a broad time period, including growth velocities during infancy and measures for the AR, in the same cohort.

However, only few of the available measurements of height and weight cover the time period when the AR typically occurs. Thus, the reliability of the estimated parameters for the AR might be affected by this sparse data (Supplementary Figure S1).

Furthermore, it should also be considered that measurement errors in height and weight might have an impact on the estimation of age and BMI at the AR and that these growth parameters are not really measured but rather derived from fitted models. However, these modelling techniques were applied in this study as these models are already established and thus comparison with results of other studies is possible. In addition, there is a certain variation of age at the corresponding physical examinations given as many of the children participated in these examinations before or after the scheduled time period. The modelling techniques applied in this study allow incorporation of unbalanced data without fixed ages at examinations.

Compared with the BMI at AR, sensitivity analyses for the association between BMI at around 5 years of age and adipokine concentrations have shown similar results. The results of other studies[40,41] also support the hypothesis that the time period at around 5 years of age is a critical period for the development of overweight and obesity as well as obesity-related factors.

A limitation of the current study was that for the majority of the children (82.5%), only non-fasting blood samples were available. Furthermore, no measures of body fat were available, and this factor may be of interest (as a confounder or effect modifier) for the relationship between growth parameters and adipokines.

A study by Taylor *et al.*[42] found an association between the time of AR and body fat. Girls who had an early AR showed a more rapid increase in body fat compared with girls with a late AR. In addition, children with an early AR had more fat mass and higher percentages of body fat at the age of 9 years although they had a similar body composition as children with a later AR.[42] Similar results were found for men aged 18–20 years in the study by Ohlsson *et al.*[11] The age at AR was inversely related to body fat mass and leptin concentrations. Considering age- and sex-specific fat mass percentiles,[43] the percentage of body fat over time shows a similar pattern as the course of BMI. Fat mass decreases during the first years of life reaching a minimum and then increases again in females but remains relatively steady in males. It has thus been shown that children with fat mass in higher percentiles have reached this minimum about 1.5 years earlier compared with children in lower body fat percentiles. On the basis of these age- and sex-specific differences in the gain of fat mass, the association between growth parameters and adipokines might be influenced by the percentage of body fat, especially between the age of the AR and leptin levels.

Although our results are based on a longitudinal modelling of growth parameters, we cannot rule out the possibility of a reverse causation effect. As only little data is available on the tracking of adipokines in children, we may only speculate as to whether adipokine levels at the age of 10 years can be considered as a good proxy for adipokine levels early in life, and consequently, whether adipokine levels early in life may affect growth. Results of some studies[44,45] have pointed towards tracking of leptin levels as the individual concentrations were in the same percentile during weight loss and regain. Moreover, the tracking was independent of the BMI. High leptin levels in relation to the fat mass affect the increase in fat mass throughout childhood.[46] However, these studies on tracking were conducted mainly in obese children.[44–46] Studies in adults also indicate a stability of adipokine levels over time.[47,48]

Adipokines, especially leptin, might also be related to diseases during adulthood. For instance, increased levels of leptin were associated with a higher risk of stroke in older men in a British study.[49] However, no associations were found between stroke and adiponectin concentrations, BMI as well as waist circumference. In addition, leptin and adiponectin might have an effect on bone formation and resorption[50] and also on the metabolic risk in men.[51]

To conclude, the results of our study indicate that an early AR and increased weight gain during infancy are associated with increased leptin concentrations during childhood. Furthermore, a positive association between the age at AR and adiponectin levels was found only among girls.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

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