Excess Early Postnatal Weight Gain Leads to Thicker and Stiffer Arteries in Young Children

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Background: Although early life growth pattern is associated with cardiovascular disease later in life, it is unknown whether vascular changes associated with excess early weight gain already occur in early childhood.

Methods: In the Wheezing-Illnesses-Study-Leidsche-Rijn (WHISTLER) birth cohort, weight and height from birth to 3 months of age were used to calculate Z-scores of individual weight and length gain rates. In the first 333 children who turned 5 years old, intima-media thickness, distensibility, and elastic modulus of the carotid artery were measured ultrasonographically. The association between weight gain rate for length gain rate (WLG), as a measure of excess weight gain, and vascular characteristics was assessed by generalized linear modeling. Interaction between birth size and WLG was tested.

Results: Per 1 SD increase in WLG, carotid intima-media thickness was 5.1 μm (95% confidence interval, 1.0–9.2; *P* value = .01) higher (adjusted for age, gender, current height, and observer). The thinner the children were at birth, the stiffer the arteries were with increasing WLG (interaction between birth size and WLG—distensibility: $P = .04$; elastic modulus: $P = .03$).

Conclusion: Excess early postnatal weight gain leads to vascular changes already in early childhood, characterized by thicker arterial walls. In children who are relatively thin at birth, excess early postnatal weight gain also leads to stiffer arteries. This supports the view that cardiovascular disease risk is associated with growth pattern early in life. **(*J Clin Endocrinol Metab* 98: 794–801, 2013)**

Early life determinants of cardiovascular disease (CVD) risk have become increasingly important in CVD prevention because CVD risk factors are a major health problem, even among children (1), and atherosclerosis starts to develop early in life (2–4).

Variations in early life growth have been associated with CVD events later in life. Not only has fetal growth been found to affect later life CVD risk (5, 6), but the importance of early postnatal growth has also been described (7–11). However, the exact mechanism is unknown. Based on the "developmental origins of health and disease" hypothesis, intrauterine exposure to undernutrition could lead to permanent metabolic changes and an adverse CVD risk in later life (5, 12).

Various studies indeed have shown the association between catch-up growth, particularly in the first 3 postnatal months (13), and CVD risk factors—for example, increased obesity (13–16) and blood pressure (BP) (17), adverse lipid profile (13, 15), and impaired insulin sensitivity (13, 15). Excess postnatal weight gain might also affect the vasculature directly. Although increased postnatal weight gain was found both to impair flow-mediated dilation in prematurely born adolescents (8) and to increase carotid intima-media thickness (CIMT) in young, low birth-

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Abbreviations: BMI, Body mass index; BP, blood pressure; CI, confidence interval; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; EM, elastic modulus; WLG, weight gain relative to length gain.

weight adults (7), neither fetal nor postnatal weight gain was associated with CIMT in preterm 19 year olds (18).

Because these studies were performed in adolescents or adults, the cardiovascular effects of postnatal growth pattern earlier in life are still unknown. Early childhood is a period in life in which the cumulative effect of other CVD risk factors might still be small. Previous studies did not account for concomitant length gain, whereas weight gain for length gain (WLG), or excess weight gain, will particularly reflect excess fat mass rather than lean mass accumulation associated with linear growth. Because most studies have been performed in premature or small for gestational age subjects (8, 18), the cardiovascular impact within a healthy pediatric population remains undetermined.

In the present study, we set out to measure CIMT and vascular stiffness in healthy young children to determine whether growth variations in the first 3 postnatal months, particularly excess weight gain, are associated with vascular structure and function in early childhood.

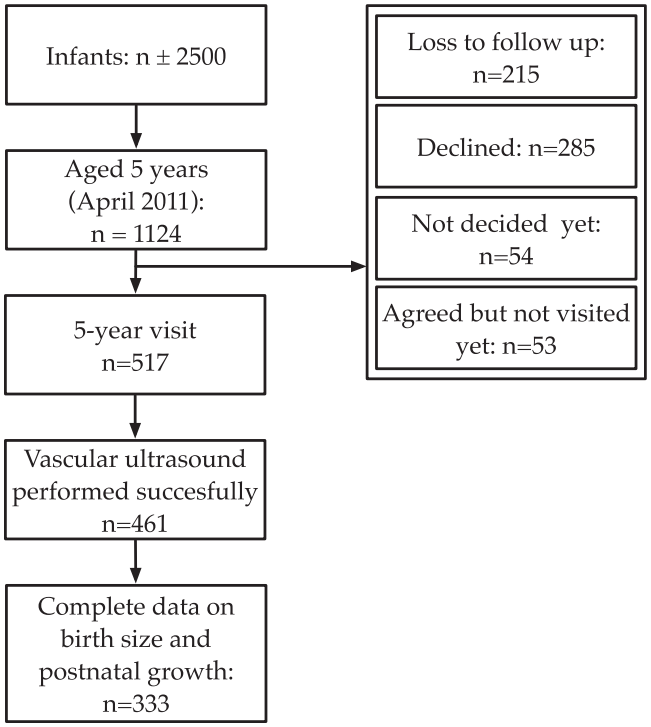

Figure 1. Flow chart of the study population.

Subjects and Methods

Design and study population

The present study is part of the Wheezing-Illnesses-Study-Leidsche-Rijn (WHISTLER) study, an ongoing population-based birth cohort on determinants of wheezing illnesses initiated in 2001 (19). Healthy newborns in Leidsche Rijn, a new residential area near Utrecht city, were enrolled. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities, and neonatal respiratory disease. In 2007 the study was extended for cardiovascular research questions (WHISTLER-Cardio). All children who had reached the age of 5 years (n = 1124 on April 26, 2011) were invited using the last-known telephone number and address for follow-up measurements. A total of 215 of the 1124 (19%) subjects were lost to follow-up, due to incorrect contact details, and 54 of 1124 (5%) have not yet been contacted. Of the remaining 855 subjects, 285 (33%) declined to take part and 570 (67%) were willing to participate, of whom 517 were measured before April 26, 2011. Vascular measurements were performed in 461 of 517 (89%) subjects. In the remaining participants, the focus was solely on respiratory measures. An overview of the study population is presented in Figure 1.

WHISTLER-Cardio was approved by the pediatric Medical Ethical Committee of the University Medical Center Utrecht. Written informed parental consent was obtained.

Neonatal visit and follow-up in infancy

Parents visited the clinic when their offspring were approximately 4 weeks of age for lung function measurements, not further described here. Birth weight and length were measured standardized in the hospital or by midwives using a standard electronic scale and an infant stadiometer. In The Netherlands, infants regularly visit Child Health Care Centers for standardized weight and length measurements. We asked parents to report these anthropometrics among others in monthly questionnaires for a period of 12 months (median number of returned questionnaires, 12). Data on parental anthropometrics, educational level, and ethnicity among others were obtained from the linked database of the Utrecht-Health-Project, a large health-monitoring study in Leidsche Rijn (20).

Follow-up in childhood

Methods of the follow-up measurements have previously been described (21). Children were reinvited at age 5 years. Conditions of the right common carotid artery were studied ultrasonographically using high-resolution echo-tracking technology (Art.lab; Esaote, Genova, Italy) including a 128-radiofrequency line multiarray, with a L10–5 40-mm linear array transducer (22). Raw radiofrequency data were analyzed online, and 6-second cineloops were stored without compression (120 Mbytes) for offline analysis. This technology gives access to all major mechanical parameters for 4-centimeter arterial segments: diastolic diameter *d*, diameter change as a function of time, so-called distension, and far-wall CIMT. CIMT and diameter were measured with 2.1-μm resolution, and distension was measured with 1.7-μm resolution (23). Subjects were measured in supine position with the head turned to the left after at least 10 minutes of resting. Both measurements were repeated a maximum of 4 times. All measurements were performed by 2 of the investigators and a trained research nurse, all blinded to other child characteristics. Reproducibility was evaluated for distension, lumen diameter, and CIMT. Mean coefficients of variation based on the multiple measurements per child for distension, CIMT, and diameter were 6.7, 6.7, and 2.3%, respectively.

During ultrasonography, BP was recorded twice in the brachial artery using a semiautomatic oscillometric device with a pediatric cuff (DINAMAP; Criticon, Tampa, Florida). Both values were averaged (see Supplemental Table 1, published on The

Endocrine Society's Journals Online web site at http://jcem.endojournals.org) to estimate common carotid artery local pulse pressure, assuming mean arterial pressure minus diastolic BP constant throughout the large arterial tree. Averages of CIMT, lumen diameter, and distension were used to assess the elastic properties of the artery as a hollow structure through cross-sectional distensibility, and of the arterial wall through the elastic modulus (EM). Both a lower distensibility and a higher EM indicate a stiffer artery. See formulas and units in Supplemental Table 1.

CIMT and distension measurements were obtained successfully in 447 of 461 (97%) and 400 of 461 (87%) subjects, respectively. In 13 of 400 (3%) subjects, distensibility could not be calculated because BP was lacking (2 subjects persistently refused, and in the first 11 participants, BP was not measured).

Additionally, weight, height, and waist circumference were measured with the participants wearing indoor clothes without shoes. Standing with the feet slightly apart, waist circumference was measured in duplicate at the level midway the lowest rib border and the iliac crest. Body mass index (BMI; kilograms/meter^2) was calculated. In addition, intraabdominal and sc fat were measured using ultrasound according to a previously described procedure (24, 25) with a Picus Pro system (Esaote), using a CA 421 convex transducer. For intraabdominal fat, the distances between the posterior edge of the abdominal muscles and the lumbar spine were measured using electronic calipers. Distances were measured from three different angles: medial, left and right lateral, with the transducer placed longitudinally on a straight line drawn between the left and right midpoint of the lower rib and iliac crest. Measurements were performed at the end of a quiet expiration. The average distance was calculated from the three angles. For all measurements, minimal pressure was applied to eliminate manual compression of tissue. Ultrasound measurements took approximately 30 minutes to complete, during which time children could watch a motion picture.

Information on child and parental characteristics with respect to the previous years was collected using questionnaires.

Infancy growth

As separate measures for early postnatal growth we used length gain rate, to reflect lean mass accumulation, and weight gain rate and weight gain rate adjusted for length gain rate, to reflect excess weight gain.

For each child with at least 2 measurements available in the first 3 postnatal months, weight gain and length gain rates were estimated using the monthly anthropometrics to reduce an effect of measurement error and individual variation over time (regression to the mean). Since the number of anthropometric measurements (median count, 3) and the age at which these were measured differed per child, the association between age and both weight and length was assessed using linear mixed modeling, allowing for individual variation in birth weight or height and growth. Because the relationship between lean body mass and height is known to be exponential (26), model fits for a linear, quadratic, and cubic model were compared, showing the best model fit for the linear model. Subsequently, to obtain individual weight gain rates, linear regression on the predicted values of the linear mixed model was performed, stratified by child. The same steps were taken to assess individual length gain rates. WLG was assessed by calculating Z-scores internal to our study population for weight gain, conditioned on length gain, using the standardized residuals from the linear regression model with weight gain as the dependent variable and length gain as the independent variable. A Z-score of +1 SD WLG indicates that the weight gain of a certain child is 1 SD larger than the mean weight gain in the population, based on that child's length gain. Model fits for a linear, quadratic, and cubic model for adjustment of WLG were compared, again showing the best model fit for the linear model.

Growth rates later in infancy were assessed as well to enable comparison of the early and late postnatal growth.

Furthermore, for birth size we derived internal Z-scores for birth weight, adjusted for birth length, gestational age, and gender.

Data analysis

Complete data on birth size, postnatal growth, and vasculature characteristics were available for 333 of 461 children (72%). Parent and child characteristics were evaluated per Z-score WLG tertiles and tested using ANOVA or Kruskal Wallis test in case of skewed data, for continuous variables and χ^2 tests for frequencies (Table 1).

We first analyzed the associations between birth size, weight gain rate, length gain rate, and WLG with CIMT, distensibility, and EM separately using generalized linear modeling. After univariable analysis, adjustments for age at follow-up, gender, and current height were made. Further adjustments were made for sonographer.

Previous studies underlined the importance of both postnatal and prenatal growth in later CVD risk (7–11). Since an association between postnatal growth and vascular properties might be modified by fetal growth, interaction between birth size, as proxy for fetal growth, and postnatal growth on vascular characteristics was tested by adding a product term of WLG and birth size, both as continuous variables, to the model.

Birth size was missing in 34 children due to missing birth length. Multiple imputation was used to impute these values, and analyses were repeated on 10 imputed datasets as sensitivity analysis.

To study whether associations between postnatal WLG and vascular characteristics were mediated by parental BMI, prenatal smoke exposure, family history of CVD before age 60 years or diabetes mellitus, breastfeeding, child's waist circumference, intraabdominal fat, or BP, these factors were added in explanatory models.

Although the focus of the present study was on early postnatal growth, the analyses were repeated with WLG in later infancy as well.

All results are expressed as linear regression coefficients with 95% confidence intervals (CIs) and corresponding *P* values. Statistical significance was considered reached at $p_{2\text{-sided}} < .05$. All analyses were performed with SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Mean CIMT, distensibility, and EM were 385.8 ± 38.2 μm (n = 323), 98.5 ± 27.0 MPa^{-1} (n = 282), and 153.6 ± 45.9 kPa (n = 272), respectively. Mean weight and length gain were 28.2 ± 4.1 g/d and 1.1 ± .047 mm/d, respectively.

Table 1. Parent and Child Characteristics per Z-Score Weight for Length Gain Rate Tertile

Range/Mean	Tertiles of Z-Score WLG in the First 3 mo After Birth			
	−2.5 to −.40/−1.0	−.40 to .41/−.02	.41 to 3.0/1.1	*P* Value
n	111	111	111	
Child characteristics				
Infancy				
Gender, % boys	51	41	48	.26[a]
Gestational age, d[b]	282 (274–288)	280 (272–287)	281 (274–286)	.32[c]
Birth weight, g	3543 ± 48	3442 ± 48	3639 ± 48	.02[d]
Birth length, cm	50.5 ± .22	50.7 ± .22	51.9 ± .22	<.001[d]
Z-score birth size, SD	.16 ± .10	−.17 ± .10	−.14 ± .10	.03[d]
Mean weight gain, g/d	24.7 ± .26	27.9 ± .26	32.1 ± .26	<.01[d]
Mean length gain, mm/d	1.1 ± .005	1.1 ± .005	1.1 ± .005	.94[d]
Breastfeeding, % ever	79	78	81	.85[a]
Exclusive breastfeeding, d[b,e]	61 (25–109)	78 (33–145)	79 (40–162)	.02[c]
Childhood				
Age at 5-y visit, y[b]	5.4 (5.2–5.5)	5.3 (5.2–5.4)	5.3 (5.2–5.4)	.29[c]
Weight, kg	19.5 ± .26	19.7 ± .26	21.5 ± .26	<.01[d]
Height, cm	114.0 ± .45	114.3 ± .45	116.4 ± .45	<.01[d]
BMI, kg/m^2[b]	14.9 (14.1–15.6)	14.9 (14.0–16.0)	15.6 (14.8–16.5)	<.01[c]
Waist circumference, cm[b]	52.3 (50.5–54.3)	51.4 (49.4–54.1)	54.0 (51.6–56.2)	<.01[c]
Intraabdominal fat, mm	36.0 ± .65	36.1 ± .66	37.0 ± .64	.49[d]
Systolic BP, mm Hg	105 ± .73	104 ± .74	106 ± .74	.12[d]
Diastolic BP, mm Hg	55 ± .68	55 ± .68	55 ± .68	.71[d]
Parental characteristics				
Maternal age at childbirth, y	32.5 ± .34	32.5 ± .34	32.0 ± .34	.53[d]
Maternal BMI, kg/m^2	25.4 ± .43	24.7 ± .42	24.8 ± .41	.47[d]
Paternal BMI, kg/m^2	25.8 ± .33	25.6 ± .32	25.7 ± .33	.92[d]
Maternal smoking, prenatal, %	6	6	1	.08[a]
Parental smoking, postnatal, %				.03[a]
Neither one of the parents	63	68	81	
One parent	29	21	17	
Both parents	9	11	2	
Socioeconomic status, % high educated at least one or both parents	79	73	70	.41[a]
Maternal ethnicity, % Western	94	93	91	.83[a]

Results are expressed as means ± SE for normally distributed continuous variables, median (25th and 75th percentiles) for skewed continuous variables, and percentages for frequencies.

[a] χ^2 test; [b] Not normally distributed; [c] Kruskal Wallis test; [d] ANOVA; [e] within those ever breastfed.

Children in the lowest postnatal WLG tertile had a higher Z-score birth size (Table 1). Although the percentage of breastfed children did not differ across the WLG tertiles, children in the lowest WLG tertile were breastfed a shorter time compared with children in the middle and highest WLG tertiles. Higher WLG was also associated with higher weight, height, BMI, and waist circumference at age 5 years. Children in the highest WLG tertile were less often exposed to tobacco smoke during pregnancy and after birth.

In Table 2 the associations between birth size, postnatal growth, and vascular characteristics are shown. Z-score birth size, derived by calculating Z-scores for birth weight adjusted for gestational age, birth length, and gender, was not associated with vascular properties. Postnatal weight gain was not associated with CIMT after adjusting for current height. However, WLG remained associated with CIMT. Per 1 SD increase in postnatal WLG, CIMT was 5.1 μm higher (95% CI, 1.0–9.2; *P* value = .01). Adjustment for arterial diameter instead of current height led to the same conclusion (data not shown). None of the postnatal growth measures were associated with arterial stiffness when analyzed separately.

The association between postnatal WLG and CIMT was not modified by birth size (*P* value for interaction, .49). However, for both measures of vascular stiffness, interaction between postnatal WLG and birth size was present. For distensibility, the thinner the children were at birth, the lower the distensibility was with increasing WLG (*P* value for interaction of .04, adjusted for confounders). For EM, the thinner the children were at birth, the higher the EM was with increasing WLG (*P* value for interaction of .03, adjusted for confounders). In Figure 2, the interaction between birth size and WLG on vasculature is presented graphically; the estimated marginal mean vascular properties with SEM are presented by WLG tertile, stratified by the median Z-score birth weight for birth length and gestational age; a low (negative) birth size Z-

Table 2. Associations Between Birth Size, Postnatal Weight for Length Gain Rate, and CIMT, Distensibility, and EM

	Linear Regression Coefficient (95% CI)		
	CIMT, μm	Distensibility, MPa^{-1}	EM, kPa
n	323	282	272
Z-score birth size, SD[a]			
Crude	0.36 (−3.8, 4.5)	1.2 (−2.0, 4.4)	−1.1 (−6.7, 4.5)
Model 1	0.34 (−3.8, 4.5)	1.1 (−2.1, 4.3)	−1.1 (−6.7, 4.4)
Model 2	0.18 (−3.9, 4.3)	1.2 (−2.1, 4.3)	−1.1 (−6.7, 4.4)
Model 3	0.25 (−3.8, 4.3)	0.79 (−2.3, 3.9)	−0.59 (−5.8, 4.6)
Weight gain, g/d			
Crude	1.7 (0.67, 2.7)[d]	−0.64 (−1.4, 0.16)	0.51 (−0.88, 1.9)
Model 1	1.3 (0.27, 2.4)[d]	−0.41 (−1.3, 0.46)	0.13 (−1.4, 1.6)
Model 2	0.98 (−0.14, 2.1)[c]	−0.13 (−1.0, 0.78)	−0.21 (−1.8, 1.4)
Model 3	0.94 (−0.18, 2.1)[c]	−0.15 (−1.0, 0.73)	−0.33 (−1.8, 1.2)
Length gain, mm/d			
Crude	−27.5 (−115.1, 60.0)	22.0 (−44.5, 88.6)	−81.6 (−196.7, 33.5)
Model 1	−35.2 (−121.9, 51.4)	30.7 (−35.8, 97.2)	−91.5 (−206.6, 23.6)
Model 2	NA	NA	NA
Model 3	−34.0 (−120.5, 52.4)	33.1 (−31.1, 97.3)	−98.4 (−207.1, 10.2)[c]
Z-score weight for length gain, SD[b]			
Crude	6.2 (2.2, 10.3)[d]	−2.5 (−5.9, 0.83)	2.9 (−2.9, 8.7)
Model 1	6.3 (2.3, 10.3)[d]	−2.5 (−5.8, 0.81)	2.9 (−2.9, 8.7)
Model 2	5.3 (1.2, 9.4)[d]	−1.7 (−5.2, 1.7)	2.0 (−4.0, 8.0)
Model 3	5.1 (1.0, 9.2)[d]	−1.9 (−5.2, 1.5)	1.8 (−3.9, 7.4)

Abbreviations: NA, not applicable. All results are linear regression coefficients with 95% CI. Model 1: Adjusted for age and gender; model 2: adjusted for age, gender, and current height; model 3: adjusted for age, gender, current height and observer (the analyses with rate of length gain are not adjusted for current height).

[a] Birth weight adjusted for birth length, gestational age, and gender.

[b] Weight gain rate adjusted for length gain rate and gender.

[c] $P \leq .10$.

[d] $P \leq .05$.

score indicates children who were relatively thin at birth, and a high (positive) birth size Z-score indicates children who were relatively thick at birth.

After multiple imputation of birth length, comparable results were found, although the associations were attenuated (data not shown).

Neither the observed associations between postnatal WLG and vascular outcomes nor the interaction with birth size were mediated by parental BMI, family history of CVD before age 60 years or diabetes mellitus, breastfeeding, or prenatal smoke exposure. A child's BP, waist circumference, and intraabdominal fat could not explain the association between WLG and CIMT either. However, the interactions between Z-score birth size and WLG on distensibility and EM were attenuated when adjusting for intraabdominal fat (*P* value for interaction, .30 and .53, respectively).

When repeating the analyses for growth in later infancy (3 to 6, 6 to 9, and 9 to 12 mo of age), no associations with vasculature were found (data not shown).

Discussion

Postnatal growth has previously been shown to be a determinant of later life CVD risk factors and CVD events (9–11, 13–15). The present study shows that among healthy young children, excess early postnatal weight gain leads to thicker arterial walls. Moreover, in children who were relatively thin at birth, excess early postnatal weight gain leads to stiffer arteries as well. To our knowledge, this is the first report of structural and functional vascular differences associated with early postnatal growth pattern this early in life.

WHISTLER is a population-based cohort, and parents with a healthier lifestyle might be more willing to participate, possibly reflected by the high level of parental education in our population. Whereas early life growth might be more frequently disturbed in lower education families, the selection in our population is unlikely to limit the generalizability or to have led to biased results because this would imply a different association between early life growth and 5-year vasculature in lower educated families. Moreover, the effect of low or differential participation in a cohort study has previously been estimated to be small (27). Children with follow-up measurements had slightly higher birth weight and were larger at birth compared to those lost to follow-up. Data on both birth size and postnatal growth were available in 64% of children in whom an ultrasound was performed. The availability of growth data was not associated with vascular characteristics. Al-

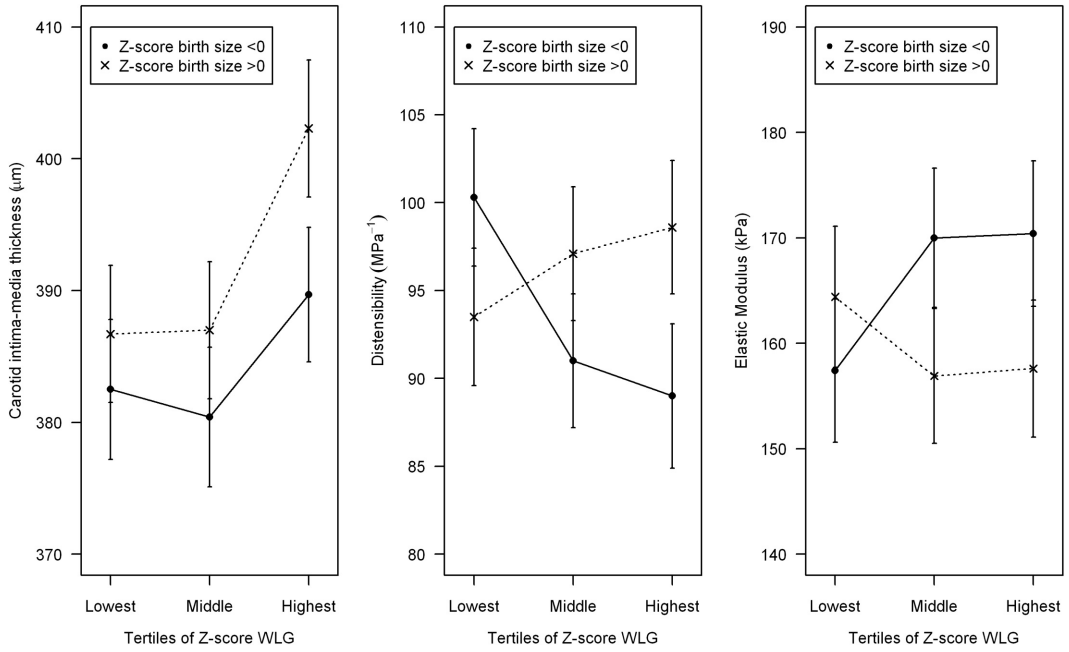

Figure 2. Results are estimated marginal means of CIMT, distensibility, and EM with SEM. Children were categorized into 6 groups based on low or high Z-score birth size (birth weight for gestational age, birth length, and gender) and tertiles of postnatal WLG; children with negative Z-score birth size were born relatively thin, and those with a positive Z-score birth size were born relatively thick. Results were obtained from linear regression models with the vascular parameters as dependent variables separately, adjusted for gender, age, and height at the 5-year visit and for observer. Corresponding p-for-interactions between Z-score birth size and WLG as continuous variables are .49 (CIMT), .04 (distensibility) and .03 (EM).

though unlikely, an effect of selective participation or follow-up cannot be ruled out completely. Since birth size was not available for all children, birth length was imputed using multiple imputation. Missing birth length was associated with lower gestational age, and the imputed values for birth length were smaller than those nonimputed. Although multiple imputation attenuated the observed associations, the same conclusions were inferred. We calculated Z-scores for weight gain rate conditioned on length gain rate based on our own population, instead of using age- and gender-specific growth charts, because our aim was to study relative differences in postnatal growth. In addition, we feel we have adjusted WLG properly because the model fits of length gain modeled quadratic or cubic were worse. Moreover, we consider our study population to be representative of a healthy pediatric population with regard to anthropometric measures because the mean infancy weights and lengths are in line with the World Health Organization growth charts (28). Since fetal growth data have not been collected in the present study, birth size was used as proxy. Because birth weight is determined by gestational age, growth potential, and intrauterine environment, birth weight adjusted for birth length and gestational age might be a better indicator of intrauterine exposures than birth weight alone. In the associations between growth and vascular properties, age, gender, current height, and sonographer were considered as confounders. Whether or not to adjust for achieved body size is a topic of discussion (29, 30). We did adjust for height at age 5 years because height is an important physiological determinant of vascular development, making current height a confounder. Adjustment for arterial diameter, as a measure of vessel size instead of current height as measure of body size, led to the same conclusions. Since ultrasonography was performed blinded to infancy characteristics and vascular properties were measured automatically with the echo-tracking device, the probability of information bias to have occurred is negligible. Additionally, we adjusted for sonographer, to further rule out the possibility of observer bias, which did not lead to substantially different results (Table 2). Although CIMT and stiffness are accepted surrogate CVD markers in adults (31) and increased CIMT relative to healthy children has been found in several pediatric patient groups with increased CVD risk (32, 33), an association between CIMT and stiffness in childhood and later CVD events can only be assumed.

The present study shows increased CIMT with excess early postnatal weight gain. Moreover, in infants born relatively small with subsequent excess weight gain, the arteries are stiffer. The fact that the association between postnatal WLG and vascular stiffness was significantly modified by birth size indicates that excess early weight gain is not associated with increased vascular stiffness in itself, but only when excess weight gain follows a period of impaired growth. This observation is in line with the

developmental hypothesis and with previous research on postnatal growth and endothelial dysfunction in preterm infants (8). In the Atherosclerosis Risk in Young Adults (ARYA) study, lower birth weight was associated with higher CIMT later in life, particularly in those with rapid postnatal growth (7). Although in the present study this interaction was observed for vascular stiffness, it was not present for CIMT. The difference in results with the ARYA study is likely explained by the difference in age of both study populations because subjects in the ARYA study were young adults. The fact that no interaction between excess early weight gain and birth size was present for CIMT could indicate that, although excess early weight gain is related to vascular structure independent of fetal growth, the consequences on vascular function are more marked when excess weight gain follows impaired fetal growth.

One possible explanation for the observed associations might be that excess early weight gain could lead to increased CVD risk factors. We have previously shown that childhood weight, BMI, waist circumference, and intraabdominal fat are related to CIMT and arterial stiffness in young children in a cross-sectional analysis (21) and that excess early weight gain is associated with BMI, waist circumference, sc fat, and likely with intraabdominal fat at 5 years of age (16). The observed differences in vasculature in the present study might be caused by increased adiposity, leading to insulin resistance and an inflammatory state by secretion of proinflammatory adipokines and cytokines (34). Although the association between excess early weight gain on CIMT remained after adjustment for adiposity at 5 years of age, the interaction between birth size and excess early weight gain on stiffness attenuated when adjusting for intraabdominal fat, suggesting an explanatory role for central adiposity. Another mechanism might be that excess early weight gain leads to vascular adaptations, such as decreased elastin synthesis in large vessels (35, 36), which could lead to increased vascular stiffness.

Although the observed vascular differences are relatively small from an individual perspective, they are relevant from a population perspective. However, we should be careful in extrapolating these findings to postnatal growth interventions because excess early weight gain might have benefits as well (37–39). Moreover, to date it remains unknown how to modify infant growth in a way that avoids adverse outcomes. Rather, based on current knowledge, prevention of known causes of impaired fetal growth and excess early weight gain, such as maternal smoking during pregnancy and formula feeding (40), is indicated.

In conclusion, excess early weight gain is associated with thicker arterial walls in childhood. Moreover, in those born thin, excess early weight gain leads to stiffer arteries as well. These results support the view that an increased CVD risk in adulthood is associated with different growth patterns early in life.

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