Rapid Early Growth May Modulate the Association Between Birth Weight and Blood Pressure at 5 Years in the EDEN Cohort Study

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Abstract—Physiological evidence suggests that birth weight (BW) and postnatal growth affect blood pressure (BP) level, independently or in interaction. Their respective roles are difficult to disentangle in epidemiological studies, however, especially when adjusting for final weight. We assessed the portion of the effect of BW on BP at 5 years that was not attributable to postnatal growth and investigated potential interactions between BW and postnatal growth velocity at different time points in the EDEN mother–child study. Collecting a median of 19 weight measurements for each of the 1119 children who completed follow-up enabled us to model instantaneous growth velocity at any age. After computing a BP SD-score at 5 years, adjusted for age, sex, current body mass index, and height, we used multiple linear regression to study its association with age- and sex-specific BW *z* score, adjusting for several maternal and pregnancy risk factors. We tested interactions between BW categories (small-, appropriate-, and large-for-gestational-age) and weight growth velocities at different ages. The BW *z* score was negatively and significantly correlated with the systolic BP SD-score at the age of 5 years (r=−0.07, P=0.02). Interactions were found between BW categories and weight growth velocities from 1 to 4 months (P from 0.002 to 0.08) but not at older ages; specifically, children born small for gestational age with a fast weight growth velocity in their first few months of life had the highest absolute systolic BP and SD score values at 5 years. They may need monitoring for cardiovascular risks. **(*Hypertension*. 2016;68:859-865. DOI: 10.1161/HYPERTENSIONAHA.116.07529.)** ● **Online Data Supplement**

Key Words: birth weight ■ blood pressure ■ body size ■ children ■ gestational age ■ risk factors

The effects of prenatal programming on blood pressure (BP) and renal function are increasingly recognized.[1] Since Barker et al[2] first reported the existence of a linear inverse relation between birth weight (BW) and BP in children and adults in the late 1980s, the numerous confirmations of this association suggest that fetal growth restriction (FGR) has a potentially deleterious effect on BP. More recently, excessive weight gain has also been associated with higher BP readings, independently of other determinants, including the infant's age, sex, height, gestational age, and the mother's prepregnancy body mass index (BMI), history of hypertension, and smoking.[3–7] However, disentangling the respective effects of BW and postnatal growth on BP while taking final weight, a major determinant of BP, into account is problematic[8]: mathematically for any given weight at BP measurement, children with lower BW will have had a faster weight growth after birth. Accordingly, standard multivariable analyses cannot distinguish the effects of low BW from those of rapid postnatal growth.[8] This phenomenon, known as the reversal paradox,[9,10] is well documented, but there are no consensual methods to avoid it.[11–13] Overcoming this paradox may be crucial for the pathophysiological interpretation of epidemiological results because both BW and growth during the first few months of life may affect later BP through mechanisms independent of final body size. Specifically, FGR is associated with impaired intrauterine development of the kidneys and reduced nephron endowment at birth.[1] A sudden change in growth velocity between the intrauterine and extrauterine periods in children with FGR could affect their vulnerable kidneys and cause glomerular hypertrophy and subsequent injury, resulting in higher BP later on.[1,14,15] We sought to develop innovative methods applying instant weight growth velocities during the first few months of life to provide epidemiological evidence supporting this hypothesis for the first time.

We, therefore, investigated the effect of BW and its interaction with early weight growth on BP at 5 years of age in the

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EDEN mother–child cohort (*Etude des Déterminants pré et post natals précoces de la santé et du développement de l'ENfant*). To be able to capture this specific effect, we used a new and straightforward method to address the reversal paradox phenomenon.

Methods

Study Design and Population

The EDEN study is an ongoing birth cohort that enrolled 2002 pregnant women before 24 weeks of gestation in 2 French university hospitals between 2003 and 2006 and followed 1907 of them through birth.[16] Exclusion criteria were multiple pregnancies, diabetes mellitus before pregnancy, illiteracy, and plans to move outside the region in the next 3 years. Among the eligible women, 53% agreed to participate. The Kremlin-Bicêtre hospital ethics committee (2002) approved the study, and women provided informed written consent at enrollment for themselves and after delivery for the newborn. Children were then followed up to the age of 5 years. After excluding 23 children with kidney or cardiac malformations and 765 who were lost to follow-up, this study analyzes data from 1119 children (Figure 1).

Data Collection

The data on the mother collected from interviews and the obstetric file included age, height, weight, BMI, sex, gestational age at birth, prepregnancy BMI, history of chronic or pregnancy-induced hypertension, social factors, and smoking status during pregnancy.

Children were examined at birth and at 1, 3, and 5 to 6 years. Their mean age at the last examination, which we will refer to hereafter as the 5-year examination, was 67.4 months. BW (in grams) was collected from the obstetric records. Heights from birth to 5 years of age were measured with standardized methods during study visits with a somatometer to the nearest 0.5 cm until the age of 1 year and thereafter with a measuring rod as they stood barefoot against a wall. They were weighed in their underwear on an electronic scale (Seca Ltd). All measurements were repeated twice and averaged. Between birth and the 5-year examination, the median (min–max) weight and height measurements were 19 (2–32) and 18 (2–31), respectively. Weight and height between these visits were also collected from child health booklets. BMI at 5 years was calculated by dividing weight (kg) by height squared (m^2). At 5 years, BP was measured with an appropriately sized cuff and an oscillometric COLIN 8800 C device, according to a standardized protocol in both centers. Children rested, lying down for 5 minutes, and then remained in that position because their BP was measured on the left arm 3× at 2-minute intervals; the mean of 3 measurements was recorded and is analyzed here.

Statistical Analyses

Student *t*- and χ^2 tests were used to compare the mother–child pairs included in the study with those excluded and lost to follow-up. We computed a noncustomized BW *z* score based on a combination of the Gardosi model for fetal growth[17] and optimal weight (sex specific at 40 weeks) based on the 1998 French National Perinatal Survey of 1998.[18] Postnatal weight growth until the age of 5 years was modeled with the Jenss–Bayley nonlinear mixed-effect model, which allowed weights and weight growth velocities to be predicted at any age from birth to 69 months, as previously described (Methods section in Material S1 online-only Data Supplement).[19] In this study, we used predicted weights and instant weight growth velocities monthly for the first 6 months of age (fastest growth period) and every 3 months afterward. Note that individual predictions of weight growth velocities were calculated independently of BW. In the multivariable analysis, we imputed missing information for maternal prepregnancy BMI (n=17) and smoking status (n=28), respectively, by the mean and the mode within the remaining population.

We assessed unadjusted and then adjusted associations between the BW *z* score and BP with the following 2 multiple linear regression models:

- Model 1: partially adjusted for sex, age, and final height
- Model 2: model 1 further adjusted for final BMI and a set of maternal and birth-related variables (prepregnancy BMI, maternal education level, history of hypertension, smoking during pregnancy, and gestational age).

Because adjusting for the child's final height and BMI may induce a reverse association between BW and BP, we next used a 2-step approach to make the appropriate adjustments while avoiding the reversal paradox. In the first step, we assessed the fraction of BP that was not attributable to final size. Stratifying by sex, we extracted the residuals of the regression of BP for height, BMI, and age (ie, the BP variability not explained by these 4 variables). After standardization of these residuals, a BP SD score was obtained and was used as the outcome in the multivariable linear regression models in the second step.

To illustrate the reversal paradox and show to what extent our method overcomes it, we calculated 3 types of Pearson partial correlations between predicted weights at different age points and:

1. Crude BP, adjusted for maternal- and pregnancy-related variables, gestational age at birth, and the child's sex and age at BP measurement;
2. Crude BP, further adjusted for final BMI and height;
3. BP SD score adjusted for the maternal- and pregnancy-related variables and for gestational age.

Finally, we investigated the associations between postnatal growth and BP at the age of 5 years by BW groups: small for gestational age (SGA), defined by a BW below the 10th percentile (BW z score <–1.282); large for gestational age, above the 90th percentile (BW z score >1.282), and appropriate for gestational age, in between. Details about these age- and sex-specific thresholds are provided in Table S1. We first tested interactions between these groups and instantaneous growth velocities in relation to crude BP. Then, we tested the interaction in relation to the BP SD score, which enabled us to remove the variability of BP attributable to final BMI and height. These interactions were studied monthly before 6 months, and every 3 months afterward. To illustrate them graphically, growth velocities were categorized into tertiles.

Interactions with sex were systematically tested in the relation between BW and BP. All statistical analyses were performed for both systolic BP (SBP) and diastolic BP (DBP). Analyses were performed with SAS 9.3 (SAS Institute Inc, Cary, NC).

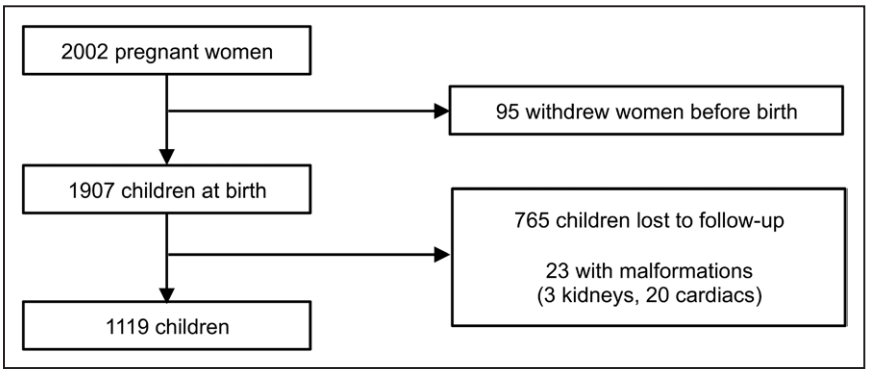

Figure 1. Flow chart of the study population.

Results

Baseline Characteristics of the Study Population

The BWs of the study children did not differ significantly from those of the children in the 1998 national perinatal survey (mean BW z score: −0.04±1.1). The SGA and large for gestational age groups each accounted for slightly >10% of the study population (Table S2). Children lost to follow-up did not differ from the study population for birth characteristics (data not shown), but participating mothers were older (30.1±4.7 versus 28.6±4.9 years, $P<0.0001$), smoked less often (20.5% versus 33.7%, $P<0.0001$), had a higher educational level (>12 years: 58.7% versus 45.9%, $P<0.0001$), and a higher rate of hypertension (2.7% versus 0.9%, $P<0.0001$).

Factors Associated With BP Level at the Age of 5 Years

There was no association between the BW *z* score and SBP in the unadjusted models (Table). Adjustment for height at the age of 5 years resulted in a nonsignificant negative association (β±SE=−0.26±0.22, $P=0.22$), which became significant after further adjustment for final BMI. Sex, final height, and BMI were the major determinants of SBP in the unadjusted and multivariable analyses. Mean SBP was higher in girls (102.7±0.3 mm Hg) than boys (101.5±0.3 mm Hg), but there was no interaction with sex in the association between BW and BP ($P>0.80$). SBP was not associated with any of gestational age, exact age at BP measurement, or maternal characteristics in the multivariable analysis.

We observed similar associations with DBP (Table S3). Mean DBP was also higher in girls (54.9±0.4 mm Hg) than in boys (53.2±0.4 mm Hg).

Correlations Between Predicted Weights Over Time and BP Level at the Age of 5 Years

In the correlations not adjusted for final BMI and height, the association between predicted weights and crude SBP at the age of 5 years increased significantly over time from 3 months of age onward (Figure 2, diamonds). Adjustment for final BMI and height induced the reversal paradox (Figure 2, squares). A negative association appeared between BW and crude SBP at the age of 5 years ($r=-0.08$, $P=0.009$), and the association between predicted weights and crude SBP was slightly lower but constant ($r=-0.07$, $P=0.01$) from 1 to 45 months. In contrast, using the SBP SD score resulted in a statistically significant negative association with weight at birth (Pearson coefficient=−0.07, $P=0.02$), which increased with age and rapidly became nonsignificant (Figure 2, triangles). Similar correlation profiles were observed with DBP (Figure S1).

Interactions Between BW Groups and Growth Velocity Tertiles Over Time in Their Relation to the BP SD Score at 5 Years

P values for interactions between BW groups and tertiles of weight growth velocities (from 1 to 4 months of age) in their relations with SBP and the SBP SD score ranged from 0.12 to 0.003 and 0.08 to 0.002, respectively. Figure 3, thus, shows that the children born SGA with the highest tertile of weight growth velocity at 4 months of age were those with the highest absolute SBP and SD score values at the age of 5 years. Interactions with weight growth velocities from 1 to 3 months were similar (data not shown). Beyond 4 months of life, these interactions, tested every 3 months, were no

Table. Maternal and Child Factors Associated With Crude Systolic Blood Pressure (mm Hg) at the Age of 5 Years

	Simple Regression Model		Multiple Regression Model 1		Multiple Regression Model 2	
Covariates	β±SE	*P* Value	β±SE	*P* Value	β±SE	*P* Value
Birth weight z score	0.01±0.21	0.97	−0.34±0.22	0.12	−0.54±0.21	0.01
Gestational age, wk					−0.21±0.14	0.13
Boy			−1.72±0.48	0.0004	−1.58±0.47	0.0008
Age at BP assessment, mo			−0.06±0.13	0.63	−0.03±0.13	0.82
Height at BP assessment, cm			0.30±0.05	<0.0001	0.23±0.05	<0.0001
BMI at BP assessment, kg/m^2					1.51±0.18	<0.0001
Maternal smoking during pregnancy					−1.03±0.60	0.08
Maternal hypertension						0.15
No hypertension					Ref	
Pregnancy-induced hypertension					1.83±1.11	
Chronic hypertension					1.64±1.43	
Prepregnancy BMI, kg/m^2					−0.04±0.05	0.44
Maternal education level, y						0.13
<12					1.11±0.58	
12					0.70±0.62	
≥12					Ref	

Results of unadjusted, partially and fully adjusted linear regressions. The EDEN Study. β±SE indicates regression parameter±SE; BP, blood pressure; and BMI, body mass index.

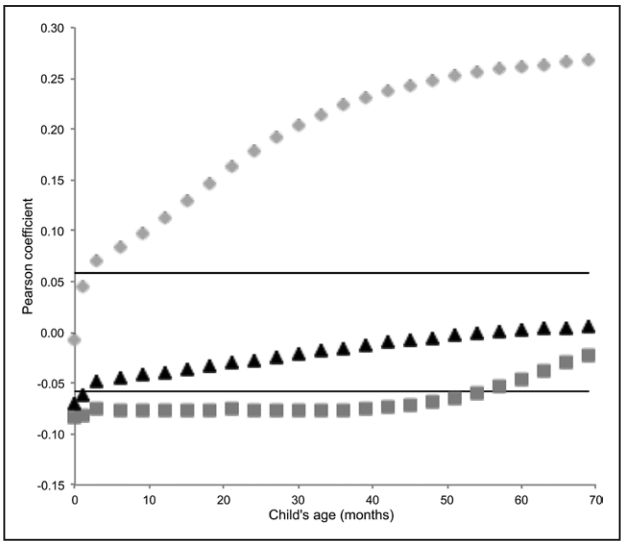

Figure 2. Trends in correlations between predicted weights over time and systolic blood pressure (SBP) level at the age of 5 years. The EDEN study. Diamonds: curve of correlations between predicted weights over time and crude SBP level, adjusted for maternal- and pregnancy-related variables, gestational age at birth, and the child's sex and age at BP measurement; squares: curve of correlations between predicted weights over time and crude SBP level adjusted for the above factors, as well as for current body mass index and height; triangles: curve of correlations between predicted weights and SBP SD score adjusted for maternal- and pregnancy-related variables and for gestational age at birth. Solid horizontal lines define areas showing statistical significance (Pearson coefficient <−0.06 and >0.06).

longer significant (P>0.35). There was no significant interaction between BW groups and any instantaneous weight growth velocity in their relations with DBP or the DBP SD score (data not shown).

Discussion

We have shown a significant negative association between BW and BP SD score at the age of 5 years that is consistent with the developmental origins of health and diseases paradigm.[2] We confirmed that this relation is independent of final body size and addressed the reversal paradox phenomenon by using a new and straightforward method. Second, we graphically illustrated the reversal paradox to help clarify this statistical phenomenon. Finally, we were able to identify a time window in the first few months of life during which fast weight gain may amplify this association in the SGA group. The pathophysiological interpretation of these findings may have clinical implications.

As expected, we found that the major determinants of BP at the age of 5 years were final height and BMI. Surprisingly, SBP and DBP were higher for girls than for boys, although a sex difference is not usually observed at this age.[4] The sex-specific mean BP levels in our study were also significantly higher than the 2004 United States charts for both SBP and DBP. This is not surprising because the oscillometric COLIN 8800 C tensiometer[20] has been shown to overestimate SBP values ≤4 mm Hg compared with a manual tensiometer, the reference device used for the US BP charts. However, we preferred to use a standardized protocol with the same oscillometric tensiometer in both centers rather than manual measurements to minimize interobserver variability, which is probably the main source of bias and error in the study of BP determinants.

Although the reversal paradox is a well-documented phenomenon, no consensus exists about methods for dealing with it. In 2005, Keijzer-Veen et al[13] addressed this issue with a method based on the unexplained variance that sought to distinguish the effect of postnatal growth from that of BW. In 2007, Tu and Gilthorpe[11] argued against this method, and in 2013, their team evaluated complex statistical methods reported to overcome the reversal paradox, but underlined the need for caution in interpreting results.[12] One of these complex methods, conditional growth modeling, has been used to study the effect of BW and growth on BP without any risk of collinearity.

We propose here a simpler model with a 2-step approach, different from the method of Keijzer-Veen et al,[13] which adjusted current weight for BW. Our method makes it possible to estimate the effect of BW on BP, independent of postnatal growth and final body size.

Figure 2 presents the correlations between weight and SBP at the age of 5 years as age increases clearly illustrates the reversal paradox phenomenon.[8] The unadjusted positive correlations between postnatal weight at any age and SBP at the age of 5 years were reversed by the adjustment for final BMI and height (Figure 2). A first interpretation might be that adjusting for body size at 5 years reveals an underlying relationship between low weight at any age between birth and 45 months and higher SBP at 5 years. However, we are unable to offer a physiological hypothesis that explains an association between a low weight at the age of 3 years (for example) and increased SBP at the age of 5 years other than a substantial weight gain between the ages of 3 and 5 years. That is, since early size is adjusted for later size, the effect of interest corresponds not only to weight at a given age but also to the opposite effect of change in size.[9] Our method allowed us to analyze the fraction of SBP variance not explained by final BMI and height (final body size) and therefore to overcome the reversal paradox. The curve of triangles in Figure 2 shows that the unexplained fraction of SBP variance was significantly negatively associated with BW, but not with subsequent predicted weights. This finding tends to confirm the specific role of FGR on children's BP levels. This modest but significant negative effect is consistent with that observed in 10-year-old children in a study that used conditional growth modeling.[5]

Recent studies suggest that children born with FGR have an increasing propensity to gain intra-abdominal fat even after completion of weight gain catch up. Given the strong relationship between adiposity and BP, epidemiological researchers have long looked for statistical interactions between BW and postnatal growth in their relations with BP, but only a few studies have succeeded in identifying any.[6,7,21] In particular, Belfort et al[7] showed that rapid increase in weight-for-length during the first 6 months of life was associated with higher early childhood SBP, particularly in children who were thin at birth. In their randomized controlled

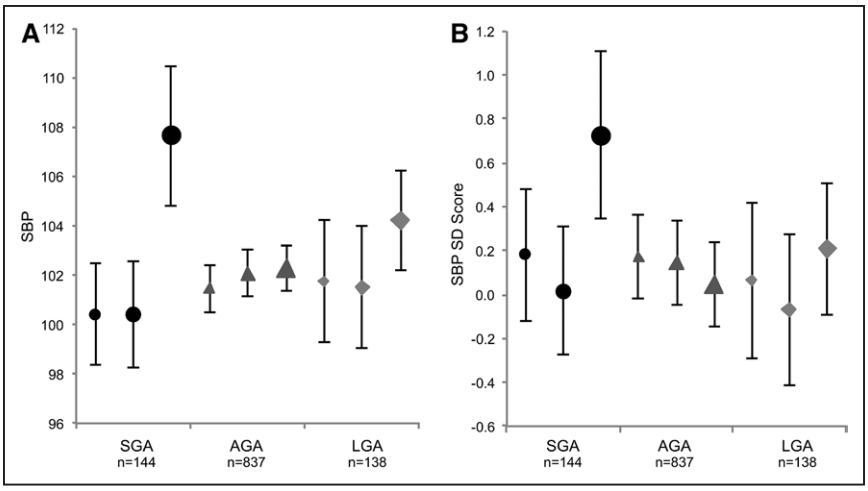

Figure 3. A, Mean of crude systolic blood pressure (mm Hg) according to tertile of instantaneous weight growth velocity at 4 mo of age, by birth weight (BW) category. Adjustment for maternal- and birth-related variables (pregestational body mass index [BMI], maternal education level, history of hypertension, smoking during pregnancy, gestational age, and sex) and age at assessment of blood pressure but not for the final body size. *P* interaction=0.003. **B**, Mean systolic blood pressure SD score (preadjusted for sex, age, BMI, and height at assessment of blood pressure) according to tertile of instantaneous weight growth velocity at 4 mo of age, by BW category. Adjustment for the same maternal and birth related variables as in **A** (excepted sex). *P* interaction=0.002. The EDEN study. BW categories: small for gestational age (SGA), circles; appropriate for gestational age (AGA), triangles; and large for gestational age (LGA), diamonds. Instantaneous weight growth velocity tertile ordered from slow (<18.7 g/d) to rapid (>21.2 g/d) within each BW category.

trial, Singhal et al[6] showed that overnutrition, through the use of enriched formula in infancy, adversely affected subsequent mean BP in children born weighing less. Figure 3A is consistent with findings from these 2 studies: among the children born SGA, those with fast weight growth during their first few months of life had a higher SBP at the age of 5 years than either those with slower weight growth or those not born SGA, whatever their growth velocity. Our similar results with the SBP SD score suggest that this interaction was not attributable to final BMI or height (Figure 3B). These results underline that it may be difficult for the kidneys of children born SGA to cope with rapid weight gain in infancy and provide complementary support to the Brenner hypothesis.[1,14,22,23] In these infants born with FGR, low nephron endowment creates renal vulnerability that may be accentuated by rapid postnatal growth in the first few months of life, which is the period of extrauterine life with the greatest growth velocity. Support for our hypothesis comes from an autopsy study that observed glomerular hypertrophy in the kidneys of neonates with low BW who died at 2 weeks of life; these findings suggest a rapid compensatory mechanism in response to the low nephron endowment and the sudden increase in renal blood flow after birth.[15] In the long term, this abnormal glomerular volume, a sign of glomerular hyperfiltration, might induce injury and, thus, increase BP. Both more evidence in humans and experimental animal studies are needed to confirm this hypothesis. Given the difficulties in evaluating the number of nephrons in humans, proxies for kidney damage must be studied, such as albuminuria or kidney size by ultrasound at different ages. The identification of similar interactions using these proxies, these BW groups, and weight growth velocities would provide evidence of our hypothesis. On the basis of such research, future interventional studies could then confirm it and perhaps establish causality.

The strengths of this study are the collection of standardized and reliable measurements of BP and of repeated weight measurements in a large, prospective, population-based cohort of pregnant women and their children. The unique contribution of this study is the use of a growth model that permitted us to compute instantaneous weight growth velocities and to estimate weight growth velocities for specific periods. This approach is clinically relevant and more precise than the standard differences in weight measurements or *z* scores over prespecified age intervals. For example, we identified an interaction on a time window with instant growth velocities that could not be found with those 2 methods (data not shown).

This study also has limitations. First, the attrition rate between inclusion and the physical examination of children at the age of 5 years was about 44%. Nonetheless, although older and more highly educated mothers tended to be overrepresented in the final sample, birth characteristics did not differ between the participating children and those lost to follow-up. Moreover, the lack of association between maternal education level (as well as for household income, data not shown) and children's SBP indicates that it is unlikely that selection bias affected our results. Second, because of the exploratory nature of our analysis for determining a risk period and the dependence between closed time point estimates, we did not correct for multiple testing. Third, as usual in epidemiology, we cannot rule out the effect of other unmeasured factors or residual confounding. Fourth, because we used tertiles of weight growth velocities to conserve a sufficient number of subjects in the interaction analyses and to highlight our initial

hypothesis, the thresholds in this study may not be specific for a deleterious growth pattern. Finally, the use of SGA in the analysis as a proxy for FGR prevented us from excluding constitutionally small children.

Perspectives

Feeding recommendations for SGA infants are vague.[24] They often consider preterm and growth-restricted neonates in the single category of low BW infants, although these pathological conditions are different.[25] A standard, albeit controversial,[26,27] goal for these babies has been weight catch-up by 1 year of age to improve neurological development. Instantaneous weight growth velocities provide a new way to study the catch-up phenomenon. We showed here that initial weight growth velocities in children born SGA seem to have an early impact on BP, possibly because of sudden hemodynamic changes in the kidneys during the perinatal period. Identifying the level of weight growth velocity that optimizes neurological development without increasing cardiovascular risk would be an important step toward prevention for SGA newborns. To meet this goal, future research should use accurate growth modeling approaches in larger representative birth cohorts. Pending new recommendations based on future interventional studies, the National High Blood Pressure Education Program Working Group[4] recommends measurement of BP in children as early as at the age of 3 years and proposes guidelines according to stage of hypertension.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study proposes a simple method to determine the fraction of the effect of birth weight on blood pressure (BP) that is not attributable to postnatal growth and final body size, via a BP SD score.
- Instant weight growth velocities from birth to age at BP measurement are used for the first time in the study of BP to consider the dynamic process of postnatal growth versus prenatal growth.

What Is Relevant?

- Our study confirms the previously described inverse relation between birth weight and systolic blood pressure SD score, consistent with the theory of the developmental origins of health and diseases.
- Our study provides a graphical illustration of the reversal paradox and, thus, helps to understand how this phenomenon works over time.
- We identified a potential time window in the first 4 months of life during which rapid weight gain might have the greatest impact on the absolute systolic blood pressure and SD score values of children born small for gestational age.
- It may suggest that a rapid weight gain in early infancy of small for gestational age babies causes difficulties for their kidneys.

Summary

The group of children who were born small for gestational age and had the highest weight growth in their first months of life had on average the highest systolic blood pressure SD score at the age of 5 years.