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ARTICLE

Birth Weight, Postnatal Growth, and Risk for High Blood Pressure at 7 Years of Age: Results From the Collaborative Perinatal Project

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ABSTRACT

OBJECTIVE. A physiologic predisposition toward hypertension is theorized to result from the combination of intrauterine growth restriction followed by rapid catch-up growth. The objective of this study was to evaluate the effects of birth weight and weight gain during childhood on the risk for high blood pressure in childhood and to identify discrete periods of catch-up growth that put children with intrauterine growth restriction at increased risk for the development of high blood pressure later in life.

METHODS. The US Collaborative Perinatal Project (1959–1974) studied 55 908 pregnancies in an observational cohort at 12 medical centers in the United States and followed the offspring through 7 years of age. All white or black children who were born at term and completed the follow-up without kidney or heart disease were included in this posthoc analysis. *z* scores were calculated for weight at birth, 4 months, 1 year, 4 years, and 7 years on the basis of study means and SD. Changes in *z* scores were calculated for each interval.

RESULTS. Each 1-kg increase in birth weight increased the odds for high systolic blood pressure by 2.19 and high diastolic blood pressure by 1.82 when race and change in weight *z* scores were also included in the regression model. An increase in weight *z* score of 1 SD above the previous weight *z* score increased the odds for high systolic blood pressure at 7 years by 1.65 (birth to 4 months), 1.79 (4 months to 1 year), 1.71 (1–4 years), and 1.94 (4–7 years) in the full model. White race increased the odds for high systolic blood pressure by 1.51.

CONCLUSIONS. In this large biracial US cohort, infants who were small for gestational age were not at increased risk for high blood pressure at 7 years of age. However, children who crossed weight percentiles upward during early childhood did demonstrate an increased risk.

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Key Words
hypertension, Barker hypothesis, catch-up growth, intrauterine growth restriction

Abbreviations
IUGR—intrauterine growth restriction
BP—blood pressure
CPP—Collaborative Perinatal Project
DBP—diastolic blood pressure
SBP—systolic blood pressure
SGA—small for gestational age
LGA—large for gestational age
AGA—appropriate for gestational age
PP—pulse pressure
OR—odds ratio
CI—confidence interval

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THE "DEVELOPMENTAL ORIGINS of adult disease" hypothesis, also known as "fetal programming," has been widely recognized as a possible mechanism for the development of a number of chronic diseases of adulthood. The hypothesis suggests that intrauterine compromise, leading to low birth weight, results in permanent alterations of fetal physiology that persist into the postnatal period.[1,2] These adaptations confer a survival advantage on the fetus while in the suboptimal intrauterine milieu, but they are deleterious to the individual after birth, when nutrients and other resources are abundant.[3,4] The hypothesized consequence is that these growth-restricted neonates grow into adults with an increased risk for chronic diseases such cardiovascular disease,[5] type 2 diabetes,[6] metabolic syndrome,[7] and osteoporosis.[8]

Because fetal growth restriction (the failure of a fetus to achieve its own growth potential) can occur in infants of any weight, the risk for the development of chronic disease is not limited to the smallest infants. There is a continuum of risk across the birth weight spectrum.[9] That risk seems to be compounded when intrauterine growth restriction (IUGR) is coupled with rapid postnatal catch-up growth. Several published reports have demonstrated the increased risk for hypertension,[10] type 2 diabetes,[11] metabolic syndrome,[12] and obesity[13] associated with the interaction between birth weight and postnatal growth.

Most of the articles that evaluated the impact of postnatal growth on subsequent health defined growth as the total amount of weight gained between birth and a second point in time. However, this crude measure of growth fails to take into account the increasing variation in weight of children as they grow and is not how pediatricians evaluate growth in normal children. For example, a girl who tracks along the 75th percentile of weight will weigh 10 kg at 1 year of age and 25 kg at 7 years of age, reflecting a weight gain of 15 kg. Another girl who tracks at the 25th percentile of weight will weigh 9 and 20 kg at 1 and 7 years of age, respectively, reflecting a weight gain of 11 kg.[14] Although the first girl gained 4 kg more than the second girl, neither girl changed her relative weight compared with her peers. In this report, we propose to define "catch-up growth" not by absolute change in weight but rather by change in relative weight compared with other children and examine the association among birth weight, catch-up growth, and blood pressure (BP) at age 7 in a large cohort of American children.

METHODS

The Collaborative Perinatal Project (CPP) enrolled pregnant women at 12 academic medical centers in the United States in a nationwide cohort between 1959 and 1965. Women were enrolled at their first prenatal visit and were followed during pregnancy, labor, and delivery. The offspring were followed for 7 years, with multiple questionnaires regarding medical and social history and detailed neuropsychological testing. Vital signs including BP were recorded before neuropsychological testing at the age 7 visit, with a manual sphygmomanometer on the right arm of the child in a sitting position. Comprehensive descriptions of the method of the study have been published previously.[15–17] Of note, the diastolic BP (DBP) measurement was taken by the fourth Korotkoff sound, as was standard procedure before 1977.[18] The data are available for public use with patient identifiers omitted from the data set.

Of the 58 960 pregnancies enrolled in the study, 51 540 mothers of white or black race were identified. We excluded all mothers who were identified as Hispanic, Asian, or other ethnicity because they composed such a small proportion of the total population. After exclusion of stillbirths, terminations, preterm births, and women who dropped out of the study before delivery, 41 413 infants were born between 37 and 42 completed weeks of estimated gestational age by menstrual dating. Of these infants, 417 died before 7 years of age, leaving 40 996 eligible children. By the end of the study, 29 973 (73%) completed the 7-year follow-up and were eligible for inclusion in this analysis.

With the use of Tukey's severe outlier criteria,[19] as well as exclusion of data points that were 4 or more SDs from the mean, biologically implausible data were removed from the data set. These criteria were applied to birth weight, head circumference, chest circumference, birth length, placental weight, SBP and DBP at 7 years of age, and weight and height at 7 years of age. Children who had a diagnosis of heart or kidney disease ($n = 109$) were also excluded, resulting in a final study population of 29 710 children.

Small for gestational age (SGA) was defined as a birth weight <10th percentile for gender, race, and gestational age using birth weight distributions based on the 29 710 children, large for gestational age (LGA) was defined as birth weight >90th percentile, and all other infants were considered appropriate for gestational age (AGA). High BP was defined as SBP or DBP >90th percentile, as recommended by the 1996 Task Force Report on High Blood Pressure in Children and Adolescents.[20] BP distributions for this study population, stratified by race and gender, were calculated, and this internal standard was used to identify children who were above the 90th percentile for SBP, DBP, or pulse pressure (PP). Maternal characteristics that are known to influence child BP were examined, including education and socioeconomic status, smoking, diabetes, and hypertension.

Childhood weight was recorded consistently at 5 times during the CPP follow-up: birth, 4 months, 1 year, 4 years, and 7 years. At each of these points, we calcu-

TABLE 1 **Maternal Characteristics**

Characteristic	Mean (SD) or %
Age, y	24.5 (6.1)
Prepregnancy BMI, kg/m^2	22.9 (4.3)
Education, y	10.9 (2.4)
White race	52.3
Smoking	46.7
Anemia (hematocrit <30%)	14.2
Type 1 diabetes >5 y	0.5
Poverty	54.6
Toxemia	2.8
Pregnancy-induced hypertension	3.4
Chronic hypertension	5.4

lated *z* scores for each recorded weight, based on study means and SDs:

The change in *z* score was calculated for each individual, generating 4 interval changes in *z* scores for each child. For example, a child who was at the 50th percentile of weight at 4 months of age but crossed percentiles to be at the 84th percentile at 1 year of age would have a change in *z* score of +1 for the interval of 4 months to 1 year. If that child continued to grow along the 84th percentile for the rest of the study, then the subsequent changes in *z* score all would be 0, because the child's relative position on a growth chart no longer changed. When a weight measurement was missing for any individual, the change in *z* score for that interval could not be calculated and the individual was not included in the regression analyses. These changes were used to assess body size in relation to the previously recorded size, thereby quantifying increase or decrease in relative size. These changes were included in multivariable logistic regression models, with birth weight and race, to predict high SBP, DBP, and PP at 7 years of age.

A preliminary logistic regression model with birth weight, race, change in weight *z* score, and predictors of IUGR (smoking, poverty, and anemia) was also created, but smoking, poverty, and anemia were not statistically significantly associated with SBP, DBP, or PP, so they were dropped from the model. Forward stepwise logistic regression technique was used, with an entry criterion of $P < .05$ and a removal criterion of $P > .10$. The models were also run on the same population stratified by birth size. A total of 24 055 infants were AGA, 2802 infants were SGA, and 2853 infants were LGA. Another set of multivariable logistic regression models were run with interaction terms between birth weight and change in weight *z* scores for each interval to determine whether size at birth and postnatal crossing of growth percentiles had a synergistic association with high BP at age 7. Statistical analysis was performed using SPSS version 11.0 software (SPSS, Chicago, IL).

RESULTS

Children who were born into this study population had a mean birth weight of 3.24 ± 0.48 kg and a gestational age of 39.7 ± 1.4 weeks on the basis of last menstrual period. Mean SBP was 102.1 ± 10.2 mm Hg, mean DBP was 61.3 ± 9.8 mm Hg, and mean PP was 40.8 ± 10.3 mm Hg.

Maternal characteristics with a potential influence on child BP are listed in Table 1. The women in this cohort were relatively young (mean: 24.5 ± 6.1 years) and thin (prepregnancy BMI 22.9 ± 4.3), with 46.7% reporting smoking and 5.4% reporting a diagnosis of hypertension at the time of presentation for prenatal care. The CPP collected data on "toxemia" rather than preeclampsia, and in this cohort, 2.8% were considered to have toxemia. During pregnancy, 14.2% of women were found to have a hematocrit <30%. Slightly more than half of these women lived below the federal poverty level, established by the US Census Bureau in 1960,[21] and the mean number of years of education was 10.9 ± 2.4. Both black and white women were well represented in this group, with 47.7% identifying themselves as black and 52.3% identifying themselves as white.

Table 2 shows the Pearson bivariate correlation coefficients for the change in weight *z* scores for each interval, as well as birth weight and BMI at 7 years of age. The purpose of Table 2 is to demonstrate that other than birth weight and growth between birth and 4 months of age, changes in growth percentiles were not strongly correlated between intervals. In other words, change in size percentile in 1 interval was not predictive of change in size percentile in other intervals. This is important because it then allows us to use the growth data for every interval together in logistic regression analysis, without the risk for collinearity.

In logistic regression analysis, we used birth weight to predict high BP at 7 years of age in an unadjusted model.

TABLE 2 **Correlation Matrix for Birth Weight and Change in Weight *z* Scores During Childhood**

Parameter	Birth Weight	Birth Weight to 4-mo Δ *z* Score	4-mo to 1-y Δ *z* Score	1- to 4-y Δ *z* Score	4- to 7-y Δ *z* Score
Birth weight to 4-mo Δ *z* score	−0.49				
4-mo to *z* score	−0.19	−0.28			
1- to 4-y Δ *z* score	−0.03	−0.11	−0.18		
4- to 7-y Δ *z* score	−0.14	−0.04	−0.05	−0.04	
BMI, 7 y	0.19	0.10	0.06	0.38	0.36

All correlations are significant at the $P < .01$ level (2-tailed).

Each 1-kg increase in birth weight increased the odds for high SBP by 1.06 (0.98–1.14; $P = .16$) and high DBP by 1.11 (1.03–1.21; $P = .007$) and widened PP by 0.95 (0.88–1.03; $P = .23$). In multivariable logistic regression, we included race and change in weight z scores throughout childhood as independent variables to predict BP. Race was added to the model because in bivariate analysis, we found that of maternal characteristics listed in Table 1, only race had a significant influence on childhood BP (data not shown). Table 3 shows regression models that predicted high SBP, DBP, and widened PP, respectively. Each 1-kg increase in birth weight adjusted for race and change in weight z scores more than doubles the risk for high SBP at 7 years of age (odds ratio [OR]: 2.19; 95% confidence interval [CI]: 1.92–2.49; $P < .001$). White race increases the odds by 1.51 (95% CI: 1.36–1.66; $P < .001$). A 1-U increase in weight z score between 2 ages increases the risk for high SBP anywhere from 1.65 to 1.94 times, depending on the interval ($P < .001$). After adjustment for race, the odds for high DBP for each 1-kg increase in birth weight were increased by 1.82 (95% CI: 1.59–2.08; $P < .001$), and white race also increased the odds, albeit modestly (OR: 1.28; 95% CI: 1.16–1.42; $P < .001$). Change in weight z scores had a positive but modest predictive effect on high DBP (OR range: 1.43–1.56; $P < .001$). Birth weight had the smallest effect on PP, with an OR of 1.22 in predicting a widened PP (95% CI: 1.06–1.39; $P = .005$). White race increased the odds by 1.46 (95% CI: 1.06–1.39), and change in weight z scores had a small positive association with widened PP (OR: 1.20–1.33; all $P < .001$). Within each of the 3 models in Table 3, the ORs for high BP per unit change in the 4 growth intervals were not statistically different from each other.

We tested the interactions between birth weight and catch-up growth by including interaction terms in regression models to predict high SBP, DBP, and PP. The interaction terms between birth weight and change in weight z score for each interval each were run in a separate model, with birth weight, race, and the 4 changes in weight z scores as the other independent variables. None of the interaction terms was found to be statistically significant (therefore, we chose not include the raw data in this article). The lack of interaction between birth weight and changes in weight z score suggests that the increased risk for high BP that is caused by rapid postnatal growth occurs to a similar degree regardless of size at birth. To illustrate this point, we stratified our analysis by size at birth (SGA, AGA, and LGA) and applied the previously described logistic regression model to predict high SBP (Table 4). We chose SBP because it is the most commonly cited measure of BP in the literature on birth weight and fetal programming. As demonstrated in Table 4, we found that an increase of 1 U in weight z score during any of the defined intervals increased the odds for high SBP to a similar degree in all 3 groups of infants. A 1-kg increase in birth weight increases the odds for high SBP by 3.53 in infants who are SGA (95% CI: 1.20–10.34; $P = .02$),

TABLE 3 Logistic Regression Models That Predict High BP and Widened PP at Age 7 Years

Risk Variable	OR[a]	95% CI	P
Dependent variable: high SBP[b] at age 7 y			
Birth weight, kg	2.19	1.92–2.49	<.001
White race	1.51	1.36–1.66	<.001
Weight gain, birth to 4 mo[c]	1.65	1.54–1.75	<.001
Weight gain, 4 mo to 1 y[c]	1.79	1.66–1.93	<.001
Weight gain, 1 to 4 y[c]	1.71	1.61–1.80	<.001
Weight gain, 4 to 7 y[c]	1.94	1.81–2.08	<.001
Dependent variable: high DBP[b] at age 7 y			
Birth weight, kg	1.82	1.59–2.08	<.001
White race	1.28	1.16–1.42	<.001
Weight gain, birth to 4 mo[c]	1.43	1.34–1.52	<.001
Weight gain, 4 mo to 1 y[c]	1.44	1.34–1.56	<.001
Weight gain, 1 to 4 y[c]	1.45	1.37–1.53	<.001
Weight gain, 4 to 7 y[c]	1.56	1.45–1.67	<.001
Dependent variable: widened PP[b] at age 7 y			
Birth weight, kg	1.22	1.06–1.39	.005
White race	1.46	1.32–1.61	<.001
Weight gain, birth to 4 mo[c]	1.20	1.13–1.28	<.001
Weight gain, 4 mo to 1 y[c]	1.31	1.21–1.41	<.001
Weight gain, 1 to 4 y[c]	1.22	1.15–1.29	<.001
Weight gain, 4 to 7 y[c]	1.33	1.23–1.43	<.001

[a] ORs reflect risk adjusted for other variables in model: birth weight, race, and 4 change in z score intervals.

[b] Defined as BP/PP >90th percentile within BP/PP distributions within the CPP population BP distributions by gender and race.

[c] OR for 1-U change in weight z scores during interval.

TABLE 4 Logistic Regression Models That Predict High SBP at Age 7 Years Grouped by Size at Birth

Risk Variable	OR[a]	95% CI	P
Infants who were SGA			
Birth weight, kg	3.53	1.20–10.34	.022
White race	1.97	1.33–2.90	.001
Weight gain, birth to 4 mo[b]	1.65	1.26–2.15	<.001
Weight gain, 4 mo to 1 y[b]	1.90	1.39–2.59	<.001
Weight gain, 1 to 4 y[b]	1.61	1.29–2.00	<.001
Weight gain, 4 to 7 y[b]	1.67	1.27–2.21	<.001
Infants who were AGA			
Birth weight, kg	2.16	1.82–2.55	<.001
White race	1.52	1.36–1.68	<.001
Weight gain, birth to 4 mo[b]	1.65	1.54–1.76	<.001
Weight gain, 4 mo to 1 y[b]	1.77	1.63–1.91	<.001
Weight gain, 1 to 4 y[b]	1.74	1.63–1.84	<.001
Weight gain, 4 to 7 y[b]	1.97	1.83–2.12	<.001
Infants who were LGA			
Birth weight, kg	3.31	1.30–8.40	.012
White race	0.99	0.64–1.51	.956
Weight gain, birth to 4 mo[b]	1.66	1.30–2.12	<.001
Weight gain, 4 mo to 1 y[b]	2.02	1.53–2.66	<.001
Weight gain, 1 to 4 y[b]	1.44	1.17–1.78	.001
Weight gain, 4 to 7 y[b]	1.89	1.48–2.42	<.001

[a] ORs reflect risk adjusted for other variables in model: birth weight, race, and 4 changes in z-score intervals.

[b] OR for 1-U change in weight z scores during interval.

2.16 in infants who are AGA (95% CI: 1.82–2.55; $P < .001$), and 3.31 in infants who are LGA (95% CI: 1.30–8.40; $P = .01$). White race increases the odds for high SBP in infants who are AGA and SGA but not in infants who are LGA (OR: 0.99; $P = .96$).

DISCUSSION

This analysis of the CPP has led us to 4 conclusions. First, infants who are SGA are not at higher risk for high BP at 7 years of age in this cohort. Second, children who cross weight percentiles upward are at increased risk for high BP in early childhood. During each childhood growth interval, there was a modest increase in the odds for high SBP at 7 years of age for each SD of increase in relative size during that interval. Third, the timing of the upward crossing of weight percentiles does not modify the risk: the increase in ORs for high SBP was similar for each of the 4 intervals that we studied, leading us to conclude that increasing growth percentiles during any period of early childhood increases the risk for high BP. Fourth, there is no interaction between size at birth and postnatal growth in predicting high BP in early childhood, on the basis of our observation that the magnitude of the effect of weight gain on BP doe not depend on size at birth.

This analysis was conducted on prospectively collected data from a large biracial cohort of pregnant women and their offspring. To our knowledge, this is the largest study of its kind conducted on a US data set, and the very large sample size makes it 1 of the few American data sets appropriate for use in studying the effect of birth size and subsequent catch-up growth in childhood on BP. The repeated weight measurements during the study follow-up made it possible to calculate change in weight z scores for 4 intervals in early childhood. This allowed us to avoid the bias that was introduced by the fact that a small neonate requires less absolute weight gain than a large neonate to maintain growth percentile. The advantage to quantifying catch-up growth by change in weight z score is the effective independence of each measure from the starting size (birth weight) and each of the other growth measures. This allowed us to consider all 4 interval measures, along with birth weight, simultaneously in our regression models.

Despite the unique nature of this study, there were several limitations to the data. Birth weight was used in this analysis as a proxy measure of fetal growth restriction, a sign that the in utero environment may have been compromised in a way that would also lead to changes in fetal physiology (programming). However, the use of birth weight <10th percentile for gestational age as a screening tool for growth restriction is less than ideal because some infants who are constitutionally small but not growth restricted will be inadvertently included in this group. Our data, like most other studies of IUGR, are subject to this limitation. Future studies using serial fetal ultrasonography or customized fetal growth curves to identify IUGR instead of birth weight are warranted.

In addition, the CPP used last menstrual period for pregnancy dating. Gross inaccuracies in dating were excluded from analysis by the removal of outlier data for gestational age and birth weight, but more subtle inaccuracies may have led to the misclassification of infants whose birth weights were borderline SGA. A previously published report demonstrated that when gestational age dating on the basis of last menstrual period indicates a pregnancy is at term, ultrasound is usually within 1 week of the menstrual estimate. However, menstrual dates are frequently in error when they indicate that the infant is either preterm or postterm.[22] Because our study included only infants with term gestation, we do not believe that the use of menstrual dating in the CPP introduces any significant error into our analysis.

A third caveat is that the CPP followed children until 7 years, an age at which only very small differences in BP are detected between individuals who later become normotensive versus hypertensive adults. These differences are expected to be amplified as the children grow older. Identifying significant differences within the tight range of BPs in 7-year-old children is compounded by the possibility of measurement error in the CPP study, which required only 1 BP measurement at the 7-year clinic visit. We have no reason to believe that this error was systematic or that it affected normal and abnormal BP differentially. Therefore, we do not expect the chance for random error in BP measurement in the CPP study to affect the results of our analysis.

Contrary to many published studies, we found that birth weight and BP later in life are positively associated.[23] The most likely reason for this discrepancy is our decision not to include current size (BMI) in the model, as many previous studies have done. We elected not to include BMI at 7 years of age in our primary model because of what is commonly known in the statistical literature as the "reversal paradox."[24] The reversal paradox refers to the seeming reversal of a statistical association (positive to negative, or vice versa) between 2 variables when a third etiologic variable is introduced into the regression model. If the third variable is actually on the causal pathway between the first 2 variables, then the inclusion of that third variable may invert the association between the other 2. As several authors have noted,[25–27] current BMI may be on the causal pathway between birth size and hypertension; therefore, the inclusion of BMI in models of birth weight that predict BP may actually reverse the seeming statistical association between birth weight and BP. In addition, it has been pointed out that BMI not only is positively related to birth weight but also is a much more powerful predictor of hypertension. Therefore, controlling for BMI in the model would cancel out the positive effects of birth

weight on BMI as well as BP.[28] We therefore chose not to include BMI in our regression model.

Our finding of a positive direction of association between birth weight and BP is comparable to other published data that do not include a measure of current weight in regression analysis.[29] What is more difficult to compare is the positive influence of postnatal growth on BP that we report here. The varied methods of quantifying catch-up growth in the literature are not easily comparable to one another. Our method of using change in *z* scores for weight has been used in at least 2 other published studies. The first reported that in a population of 346 British men and women, an increase in weight *z* score between birth and 1 year or between 1 year and 5 years did not increase SBP or DBP at 22 years of age (with or without adjustment for adult BMI).[30] Our results may have differed for 1 of several reasons: we used tighter age intervals, examined childhood BP, and had a population that included both white and black Americans. The second study reported that in a population of 749 Brazilian adolescents, an increase of 1 U of weight *z* score per year resulted in an increase in SBP of 0.37 mm Hg at 15 years of age, and weight gain in infancy, childhood, or adolescence had the same implications on BP.[31] This positive and similar effect of weight gain at different intervals of childhood growth on BP is comparable to our results.

CONCLUSIONS

On the basis of our data, an increase in growth percentile during the first 7 years of life puts a child at increased risk for high BP in early childhood. Because BP tends to track over a lifetime, this rapid growth has implications for adult hypertension.[32,33] There is a continuum of risk for hypertension across the birth weight spectrum, so we must carefully consider the wisdom of encouraging rapid weight gain in any of our patients, including but not limited to infants with IUGR and preterm infants, in light of their future health. Future research should attempt to determine in which children catch-up growth is actually "excess growth" and which infants and children would benefit by maintaining their growth percentiles through childhood and beyond. Clearly, additional study is important for both pediatric and adult health.

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