Racial Disparities in the Association between Birth Weight in the Term Infant and Blood Pressure at Age 7 Years: Results from the Collaborative Perinatal Project

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BP has been inversely associated with birth weight in studies worldwide, but few studies have included black individuals. The US National Collaborative Perinatal Project followed 58,960 pregnant women and their resultant offspring for 7 yr. In this *post hoc* analysis, all term white or black children without kidney or heart disease were included ($n = 29,710$). The effect of birth weight and other risk factors on systolic (SBP) and diastolic BP (DBP) was evaluated at 7 yr. Mean birth weight and body mass index at 7 yr were slightly lower for black compared with white children (birth weight 3.14 ± 0.48 *versus* 3.32 ± 0.46 kg [$P < 0.001$]; body mass index 15.8 ± 2.0 *versus* 16.3 ± 2.0 [$P < 0.001$]). Compared with white mothers, black mothers were less likely to smoke (41 *versus* 52%), were more anemic (23 *versus* 7%), and were more likely to live in poverty (72 *versus* 39%). In linear regression, there was significant interaction between race and birth weight in predicting SBP ($P = 0.002$). In bivariate analysis, birth weight was positively associated with SBP ($\beta = 0.87$) and DBP ($\beta = 1.14$) in black children ($P < 0.001$) but not associated with either in white children. With maternal poverty, educational level, and anemia during pregnancy added to the model, birth weight remained a significant positive predictor of SBP ($\beta = 0.89$, $P < 0.001$) in black but not in white children ($\beta = 0.02$, $P = 0.17$). The association between birth weight and SBP differs between black and white children. The cause of intrauterine growth restriction–associated hypertension seems to be race sensitive; therefore, future studies of racial disparities in the "Barker hypothesis" may help in the understanding of the mechanism of fetal programming of hypertension.

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Low birth weight, as an indicator of fetal growth restriction, has been associated recently with a number of chronic diseases in adult life. First widely publicized by Barker (1,2) in Great Britain, the "fetal programming," or "fetal origins of adult disease," hypothesis states that intrauterine compromise results in permanent alterations in fetal physiology. These adaptations may confer a survival advantage on the fetus while in a suboptimal intrauterine milieu but are deleterious to the individual after birth when nutrients and other resources are abundant (3,4). The hypothesized consequence is that growth-restricted neonates develop into children and adults with an increased risk for chronic diseases such cardiovascular disease (5), type 2 diabetes (6), metabolic syndrome (7), and osteoporosis (8).

The body of evidence from epidemiologic studies of this hypothesis is largest in support of a relationship between low birth weight and hypertension later in life. A widely referenced meta-analysis of these studies (9) concluded that birth weight is inversely related to BP, most strongly in the pre- and postadolescent periods, but the overwhelming majority of these studies were conducted in primarily white populations, with very little ethnic diversity. Of the 80 studies included in the meta-analysis, only three focused primarily on populations of African descent.

While reviewing the literature, we identified two studies of the relationship of size at birth and BP that directly compared black and white individuals. The Alabama Successive Small for Gestational Age Study (10) examined the relationship between intrauterine growth restriction (IUGR) and BP at age 5 yr and found that whereas white children had an inverse relationship between birth weight and BP, black children had a direct association. In contrast, the Bogalusa Heart Study (11) reported on 185 teenagers who were aged 15 to 17 yr and found an inverse

This paper, documenting gender differences in response to renin-angiotensin system (RAS) blockade, adds to the complexities of interpreting the specificity of RAS blockade in treating progressive renal disease, which is reviewed in depth by Griffin et al. *in the accompanying issue of* CJASN *(Griffin* et al., *pages 1055–1065).*

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relationship for both white and black. These contrasting results and the paucity of data on black individuals in general suggest that more attention should be paid to potential racial disparities in the fetal programming of hypertension. We therefore undertook a study in a large biracial American cohort to examine the association between birth weight and BP at age 7 yr in both black and white populations and additionally to examine how current body mass index (BMI; which may be in the causal pathway of hypertension) affects the association between birth weight and BP in both groups.

Materials and 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 yr, with multiple questionnaires regarding medical and social history and detailed neuropsychological testing at 4 and 8 mo and 1, 3, 4, and 7 yr of age. 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 (12–15). 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 ere identified as Hispanic, Asian, or other ethnicity because they composed such a small proportion of the total population. After exclusion of stillbirths, terminations, premature births, and women who dropped out of the study before delivery, 41,413 infants were born between 37 and 42 completed weeks' estimated gestational age by menstrual dating. Of these infants, 417 died before age 7 yr, leaving 40,996 eligible children. By the end of the study, 29,973 (73%) completed the 7 yr follow-up and were eligible for inclusion in this analysis.

Using Tukey's severe outlier criteria (16) as well as excluding data points that were 4 SD or more from the mean, we removed biologically implausible data from the data set. These criteria were applied to birth weight, head circumference, chest circumference, birth length, placental weight, systolic (SBP) and diastolic BP (DBP), weight, and height at age 7 yr. Children who had a diagnosis of heart or kidney disease ($n = 109$) also were excluded, resulting in a final study population of 29,710 children.

For bivariate analysis, infants with IUGR were defined by a birth weight <10th percentile for gender, race, and gestational age using birth weight distributions that were based on the 29,710 children. Bivariate analyses implemented t test and χ^2 tests where appropriate. Multivariable linear regression models were constructed to predict SBP in this population from risk factors that were identified in bivariate analysis. An interaction term between race and birth weight also was included to determine whether the effect of birth weight on BP depends on race. Forward stepwise linear regression technique was used, with an entry criterion of $P < 0.05$ and a removal criterion of $P > 0.10$. Although child gender, maternal smoking, chronic hypertension, prepregnancy BMI, and diabetes were not significantly associated with childhood BP in bivariate analysis, we chose to include them *a priori* in the model but found that these variables were dropped from the model during the forward stepwise logistic regression procedure. We also decided (*a posteriori*) to include a measure of accelerated weight gain in early childhood: The change in z score for weight between ages 4 and 7 yr. Childhood weight was recorded consistently during the CPP follow-up at ages 4 and 7 yr. At both of these points, we calculated z scores for each recorded weight, on the basis of study means and SD:

$$\text{Z score} = \frac{\text{recorded weight} - \text{mean weight}}{\text{standard deviation}}$$

The z score allows for standardization of weight, with a mean of 0 and an SD of 1. The change in z score was calculated for each individual to assess the acceleration or deceleration of weight gain, relative to the rest of the population.

Results from the multivariable linear regression models are reported as β coefficients (the increase in SBP that results from a 1-unit increase in the predictor variable, given that all other variables in the model are held constant) and 95% confidence intervals (CI). All statistical analysis was performed using SPSS version 11.0 software (Chicago, IL).

Results

The women who were included in this analysis were relatively young and thin, with a mean age of 24.5 yr (SD 6.1 yr) and a mean prepregnancy BMI of 22.9 (SD 4.3). Almost half of this population smoked during pregnancy (46.7%), with a mean self-reported daily cigarette consumption of 5.8 cigarettes per smoker. Chronic hypertension before pregnancy was reported by 5.4% of mothers. During pregnancy, 2.8% of mothers developed preeclampsia, 0.7% received a diagnosis of gestational diabetes, and 2.5% had pregnancy-induced hypertension. Approximately 54% of women who enrolled in the CPP study were below the poverty level, based on US Census Bureau standards for family income from 1960 to 1970 (17). The mothers had a mean education level of 10.6 ± 2.6 yr.

The characteristics of mothers by race are presented in Table 1. Of the 29,710 mothers who were included in this analysis, 14,171 were black and 15,539 were white. Overall, black mothers were younger (24 *versus* 25 yr), were heavier (prepregnancy BMI 23.3 *versus* 22.4), and had fewer years of education (10.3 *versus* 11.4 yr) than their white peers. They also were less likely to smoke (40.5 *versus* 52.3%), more likely to be anemic (22.9 *versus* 6.9%), and more likely to live in poverty (72 *versus* 39%). All of these comparisons were significant at the $P < 0.001$ level by t test or χ^2 test and were persistent when mothers of infants with and without IUGR were studied separately.

Table 2 demonstrates the characteristics of the offspring of these mothers, grouped by race. Black term infants had a lower mean birth weight than white term infants (3.14 *versus* 3.32 kg) as well as significantly lower mean SBP and DBP than the white infants at the 7-yr follow-up. However, pulse pressure was comparable across racial groups (40.9 mmHg white and 40.8 mmHg black). BMI at age 7 yr was significantly lower for black children in this study than for white children (15.8 *versus* 16.3). All of these comparisons were significant at the $P < 0.001$ level by t test or χ^2 test and were persistent when infants without IUGR were studied separately. When only infants with IUGR were considered, there were no significant differences in birth weight between black and white infants, but the differences between the races in SBP, DBP, and BMI at 7 yr were persistent.

The relationship between birth weight and BP is strikingly different in black and white children. In black children, bivariate analysis demonstrates a significant relationship between birth weight and both SBP ($\beta = 0.9$; 95% CI 0.5 to 1.2; $P < 0.001$) and DBP ($\beta = 1.1$; 95% CI 0.8 to 1.5; $P < 0.001$). However, in white children, neither SBP ($\beta = -0.03$; 95% CI −0.4 to 0.3; $P = 0.87$) nor

Table 1. Maternal characteristics[a]

Characteristic	Total Group		Non-IUGR Group		IUGR Group	
	Black	White	Black	White	Black	White
n	14,171	15,539	12,878	14,724	1293	815
Age (yr)	24.0 ± 5.9	25.0 ± 6.3[b]	24.0 ± 6.3	25.0 ± 5.9[b]	23.4 ± 6.6	24.7 ± 5.9[b]
Prepregnancy BMI	23.3 ± 4.7	22.4 ± 3.9[b]	23.5 ± 4.7	22.5 ± 3.9[b]	22.1 ± 4.4	21.5 ± 3.7[b]
Education (yr)	10.3 ± 2.1	11.4 ± 2.5[b]	10.3 ± 2.1	11.4 ± 2.5[b]	10.1 ± 2.2	10.8 ± 2.4[b]
Smoking	40.5%	52.3%[b]	39.2%	51.0%[b]	54.1%	76.1%[b]
Anemia	22.9%	6.5%[b]	23.0%	6.6%[b]	22.6%	5.3%[b]
Type 2 diabetes > 5 yr	0.1%	0.7%[b]	0.1%	0.7%[b]	1.2%	0.6%[b]
Gestational diabetes	1.1%	1.0%	1.0%	0.9%	0.7%	0.5%
Poverty	72.0%	39.0%[b]	72%	38.7%[b]	74.7%	45.0%[b]
Hypertension < 24 wk	1.0%	0.8%	0.9%	0.8%	2.1%	1.3%
Hypertension > 24 wk	2.7%	2.4%	2.4%	2.3%	5.4%	4.2%

[a]BMI, body mass index; IUGR, intrauterine growth restriction.
[b]$P < 0.001$ by *t* test or χ^2.

Table 2. Child characteristics[a]

Characteristic	Total Group		Non-IUGR Group		IUGR Group	
	Black	White	Black	White	Black	White
n	14,171	15,539	12,878	14,724	1293	815
Gestational age (wk)	39.5 ± 1.4	39.9 ± 1.4[b]	39.5 ± 1.4	39.9 ± 1.4[b]	39.7 ± 1.4	39.8 ± 1.4[b]
Birth weight (kg)	3.14 ± 0.48	3.32 ± 0.46[b]	3.22 ± 0.40	3.37 ± 0.43[b]	2.36 ± 0.25	2.38 ± 0.23
SBP (mmHg)	101.4 ± 10.2	102.7 ± 10.1[b]	101.5 ± 10.2	102.7 ± 10.1[b]	100.5 ± 10.4	102.7 ± 10.8[b]
DBP (mmHg)	60.6 ± 10.1	61.9 ± 9.5[b]	60.7 ± 10.0	61.9 ± 9.5[b]	59.6 ± 10.3	61.8 ± 9.8[b]
PP (mmHg)	40.8 ± 9.9	40.9 ± 10.7	40.8 ± 9.8	40.9 ± 10.7	40.9 ± 10.3	41.0 ± 11.2
BMI at 7 yr	15.8 ± 2.0	16.3 ± 2.0[b]	15.9 ± 2.0	16.3 ± 2.0[b]	15.2 ± 2.0	15.8 ± 2.0[b]
Male	49.7%	51.2%	49.9%	51.5%	48.1%	46.4%
SBP > 90th percentile	10.7%	10.6%	10.8%	10.6%	9.9%	10.8%

DBP, diastolic BP; PP, pulse pressure; SBP, systolic BP.
[b]$P < 0.001$ by *t* test or χ^2.

Table 3. Linear regression model including interaction term between birth weight and race predicting SBP at age 7 yr[a]

	β Coefficient	95% CI	*P*
Birth weight (kg)	0.88	0.48 to 1.28	<0.001
White race	4.05	2.30 to 5.80	<0.001
Birth weight × race	−0.86	−1.40 to −0.33	0.002
Poverty (yes)	0.54	0.26 to 0.81	<0.001
Maternal education (yr)	−0.22	−0.27 to −0.16	<0.001
Maternal anemia (yes)	−0.10	−0.47 to 0.28	0.61

[a]CI, confidence interval.

DBP ($\beta = 0.2$; 95% CI −0.2 to 0.5; $P = 0.3$) is related to birth weight.

To examine further the interaction between birth weight and race, we used linear regression with an interaction term between birth weight and race to predict SBP at age 7 yr. This model is described in Table 3. With maternal poverty, education, and anemia included in the model, the interaction between birth weight and race is significant ($P = 0.002$). Of note, maternal anemia is not a strong predictor of childhood BP, but poverty and less education are ($P < 0.001$ for both). In Table 4, separate models for black children, white children, and the total study group without an interaction term are presented. With maternal factors such as poverty, educational level, and anemia included in the model, birth weight remains a significant positive predictor of SBP in black children ($\beta = 0.89$; $P < 0.001$) but not in white children ($\beta = 0.02$; $P = 0.17$). Although we did not include weight gain in Table 4, we did run each model with a *z* score for weight gain between ages 4 and 7 yr. When weight gain *z* score is added to each model, there is no change in the significance or direction of the relationship between birth weight and BP in black children ($\beta = 0.61$; $P < 0.01$) and white children ($\beta = 0.00$; $P = 0.96$).

Because much of the literature on birth weight and subsequent

Table 4. Linear regression models predicting SBP at age 7 yr, not including BMI at age 7 yr

	Black		White		Total Group	
	β	95% CI	β	95% CI	β	95% CI
Birth weight (kg)	0.89	0.49 to 1.30[a]	0.02	−0.33 to 0.37	0.40	0.13 to 0.66[a]
White race					−1.23	−1.55 to −0.99[a]
Poverty (yes)	0.01	−0.41 to 0.43	−0.97	−1.33 to −0.61[a]	−0.54	−0.82 to −0.27[a]
Maternal education (yr)	−0.08	−0.17 to −0.01[a]	−0.31	−0.38 to −0.24[a]	−0.22	−0.28 to −0.17[a]
Maternal anemia (yes)	0.03	−0.42 to 0.47	0.27	−0.42 to 0.96	0.09	−0.28 to 0.46

[a] $P < 0.001$.

BP has taken into account the BMI of the individual at the time of BP measurement, we ran our regression model with an additional predictor variable: BMI at age 7 yr. In this new model (Table 5), the addition of BMI at 7 yr caused the relationship between birth weight and SBP to invert and become nonsignificant in black children ($\beta = -0.28$; $P = 0.06$) and caused the relationship to invert and become significant in white children ($\beta = -0.97$; $P < 0.001$).

Discussion

This study of the association between birth weight and BP at age 7 yr detected statistically significant differences in the relationship between size at birth and BP between white and black children in the United States. In black children, higher birth weight was associated with higher SBP at 7 yr, whereas no association was found between birth weight and BP in white children. Contrary to previous reports in the literature, we did not find an inverse relationship between birth size and BP, and the direct relationship that we found depended on race. A similar race-dependent direct relationship was noted in a sample of 197 black children compared with 65 white children at age 5 yr from the Alabama Successive Small for Gestational Age Study (10), so our findings are in accordance with at least one other published report.

Lack of Evidence for an Inverse Relationship between Birth Weight and BP

Because BP tends to track throughout the life course (18,19), a very small increase in risk at age 7 yr may be amplified in middle and older age. This is the basis for examining BP in childhood as a predictor of clinically significant hypertension later in life. The caveat of this approach is that BP increases in childhood are relatively small and difficult to detect, and this may explain why we did not detect an inverse relationship between birth weight and BP at age 7 yr.

Another potential reason for this result may be a methodologic issue resulting from our decision not to include current size (BMI) in the model, as many previous studies have done. There is an ongoing debate in the literature regarding the validity of controlling for size at the time of BP measurement when modeling the relationship between birth size and subsequent BP. Most common, this is measured as BMI. We elected not to include BMI at age 7 yr in our primary model, because of what is commonly known in the statistical literature as the "reversal paradox" (20). The reversal paradox refers to the apparent reversal of a statistical association (positive to negative, or *vice versa*) between two variables when a third causative variable is introduced into the regression model. If the third variable actually is on the causal pathway between the first two variables, then the inclusion of that third variable may invert the association between the other two. As several authors have noted (21,22), 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 actually may 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 than birth weight is. Therefore, controlling for BMI in the model would cancel out the positive effects of birth weight on BMI as well as BP (23). We therefore chose not to include BMI in our regression model.

Most of the published models that predict BP from birth weight

Table 5. Linear regression models predicting SBP at age 7 yr, including BMI at age 7 yr

	Black		White		Total Group	
	β	95% CI	β	95% CI	β	95% CI
Birth weight (kg)	−0.28	−0.67 to 0.12	−0.97	−1.32 to −0.63[a]	−0.68	−0.94 to −0.42[a]
BMI at 7 yr	1.35	1.26 to 1.44[a]	1.57	1.49 to 1.66[a]	1.47	1.41 to 1.53[a]
White race	−0.87	−1.13 to −0.60[a]				
Poverty (yes)	0.33	−0.08 to 0.74	−0.83	−1.17 to −0.48[a]	−0.32	−0.58 to −0.06[b]
Maternal education (yr)	−0.12	−0.21 to −0.03[b]	−0.25	−0.32 to −0.18[a]	−0.20	−0.25 to −0.15[a]
Maternal anemia (yes)	0.24	−0.20 to 0.66	0.54	−0.12 to 1.20	0.34	−0.02 to 0.695

[a] $P < 0.001$.
[b] $P < 0.01$.

have included current weight or BMI, making comparisons with our own models difficult. To allow comparison, we created a linear regression model of SBP with birth weight, race, the interaction between birth weight and race, BMI, poverty, maternal education, and anemia as independent variables. It is interesting that when we opted to include current size in the model, we did indeed find a reversal paradox. The addition of BMI to the model caused the association between birth weight and SBP to invert and become nonsignificant in black children. In white children, the addition of BMI at age 7 yr caused the relationship between birth weight and SBP to become inverse and statistically significant, just as widely reported in the early Barker hypothesis literature (9). The interaction between birth weight and race continued to be statistically significant in the BMI-inclusive model, demonstrating that even while controlling for current size, black and white children differed. The reversal paradox, now suspected of creating spurious inverse associations between birth weight and BP, is apparent in our data. As a result, we did not include a measure of current size in our primary regression models.

Racial Disparity in the Relationship between Birth Weight and BP

The interaction between race and birth weight in predicting BP may reflect the influence of hereditary and postnatal factors that have not been accounted for in our regression model or an inherent racial difference in the physiologic mechanism of fetal programming. Because the mechanism is as yet undefined, it is difficult to explain the racial differences that we found in terms of physiology, but the epidemiologic evidence for a racial disparity may help us sort through the many hypothesized mechanisms of *in utero* programming of BP.

The racial disparity may reflect postnatal or genetic influences that can be associated with race, such as socioeconomic status, education, and diet. We were able to control for proxy measures of these factors, namely, family poverty status, educational level of the mother, and anemia during pregnancy (which reflects in part the protein and iron intake of the mother). Including these factors in our regression model resulted in a persistent association between birth weight and SBP in black children and a continued lack of association between the two in white children. Other maternal influences that may be associated with race, namely, maternal smoking, prepregnancy BMI, chronic hypertension, and diabetes, were included initially in the regression model but were not statistically significant predictors of high BP and were dropped from the model. Finally, accelerated weight gain in early childhood as a predictor of BP was evaluated by including standardized weight gain between ages 4 and 7 yr in our models stratified by race. We found that an accelerated weight gain during this interval indeed was a predictor of BP at age 7 yr, but the inclusion of this variable did not change the significance or the direction of any of the previously mentioned associations among white and black children alike.

The evidence for fetal programming of BP in black populations has been limited. In Africa, small studies of children in South Africa (24), Zimbabwe (25), and Gambia (26) suggested an inverse relationship between birth weight and BP when current body size was included in the model. In one Nigerian study (27), no statistical association was noted, regardless of whether BMI was included as an independent variable. The largest published study thus far of black populations is from Jamaica (28), where 1610 children who were aged 6 to 16 were found to have an inverse relationship between birth size and BP when current size was controlled in the model. In the United States, three studies of black individuals have examined this relationship: In Alabama (10), Bogalusa (11), and Philadelphia (29). It is interesting that, all three reported very different results. The Bogalusa cohort consisted of 185 white and black children who were aged 15 to 17 yr. Both white and black children in the study had an inverse birth weight–BP relationship (including current BMI in the model). The Alabama study included 262 white and black children who were aged 5 yr and found a racial disparity: After controlling for BMI, white children had an inverse birth weight–BP relationship, whereas black children had a direct relationship. Our results are in agreement with these. In Philadelphia, in a cohort that was based on the original Philadelphia cohort but followed past the study period until 28 yr of age, there was no statistically significant association between birth weight and BP in 137 black individuals. Because of the relatively small sample size, there was insufficient power to look at BP in individuals of the highest birth weights, but the authors commented that a disproportionately high number of individuals in the highest birth weight category had borderline hypertension at age 28 yr. This observation is consistent with the results of our data analysis, based on the national CPP cohort at age 7 yr.

The racial disparity noted here argues against the hypothesis that the high prevalence of hypertension in the black community may be accounted for by the high prevalence of low birth weight in that community. In fact, in this study population, the high birth weight black infants seem to be the ones who are at increased risk for high BP. This divergence in the relationship between birth size and BP suggests that the pathophysiology of hypertension that is programmed during the fetal period is race specific and may have a genetic component. The hypothesis of oligonephropathy that is caused by fetal growth restriction and leads to hyperfiltration, scarring, and eventual hypertension seems less likely in this scenario, particularly given that oligonephropathy has not been related to race (30). Possible explanations include a disturbance in salt or glucocorticoid sensitivity, through programming of the renin-angiotensin (31), endothelin (32), and kallikrein-kinin systems (33). These systems all have noted racial differences, which may be affected by fetal growth.

This study adds to the growing body of evidence that suggests that public health initiatives to prevent chronic diseases such as hypertension may need to begin as early as the prenatal and early childhood periods. Exploring racial disparities in the developmental origins of health and disease is a critical step toward understanding the mechanisms of fetal programming and eventually developing interventions against chronic disease.

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