Racial disparities in the association of foetal growth retardation to childhood blood pressure

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Abstract

Background. Foetal growth retardation (FGR), defined as less than the 10th percentile of birth weight for gestational age, is reported to be an important contributor to hypertension and cardiovascular disease in children and adults, but findings are not consistent. For this reason we re-examined the role of FGR in childhood blood pressure.

Methods. We performed univariate and multivariate analyses on data gathered from 262 children, age 5 years, born to mothers at risk for pre-term delivery or FGR infant. The characteristics of the mothers and the children were evaluated using Student’s t-test. Rates and proportions were compared using either χ²-square or Fisher’s exact test. Linear regression models evaluated the effect of birth weight and body mass index on systolic and diastolic blood pressure. Multivariate linear regression was used to model the effects of FGR, gestational age, body mass index, race, gender, maternal smoking, maternal gestational diabetes on blood pressure while adjusting for possible confounders.

Results. Systolic blood pressure was inversely associated with birth weight in white children while a small direct association was noted in African Americans. Body mass index was positively associated with systolic blood pressure in both groups. Multiple linear regression analyses showed FGR and early gestational age were associated with higher blood pressure in white but not African American children, accounting for a 13.2 mmHg difference between FGR and appropriate for gestational age groups. Blood pressure in African Americans was strongly affected by maternal gestational diabetes and smoking.

Conclusions. Birth weight influences childhood blood pressure but the effects may vary depending on ethnic group. The relative importance of birth weight on blood pressure may depend on other prenatal and post-partum risks.

Keywords: birth weight; blood pressure; children; foetal growth retardation; race

Introduction

Of the numerous physiologic, genetic and environmental factors influencing blood pressure, there is sustained interest in a possible contribution of low birth weight to adult and childhood hypertension. Studies suggest foetal growth retardation (FGR) may pre-program children for subsequent hypertension, cardiovascular and renal disease [1,2]. Such studies have demonstrated statistical associations between low birth weight and/or gestational age and hypertension as well as cardiovascular and renal disease in adults and in children [1–5]. However, in other studies such associations have been weak or else were not found [6–11].

The previously mentioned studies mostly examined white populations, whereas the prevalence of low birth weight is much higher in people of African descent [12]. Thus, it has been proposed that FGR, defined as less than the 10th percentile of birth weight for gestational age, might partly explain the high prevalence of hypertension and renal disease in African Americans [13]. Data from a recent study of South African black children support that view [14]. In contrast, no association between FGR and higher blood pressure was found in Nigerian children [15]. Moreover, such an association has not been reported in African American children [7,9–11] or young adults [7]. The absence of a consistent association between low birth weight and blood pressure has raised questions about the relative importance of low birth weight in the genesis of hypertension and subsequent renal and cardiovascular disease [16].
Since longitudinal studies have shown that blood pressure in childhood and adolescence may predict blood pressure in adult life, we felt it important to re-examine the role of birth weight, especially FGR, in determining childhood blood pressure, particularly since it may contribute to the well-established racial differences in hypertension and renal disease risk. In order to assess the influence of FGR and gestational age on blood pressure, we reviewed data of 5-year-old children, well characterized with regard to gestational age and blood pressure, born to mothers at high risk for having a growth retarded infant.

Subjects and methods

The study is an analysis of data that were collected in the Successive Small for Gestational Age Study that included women who enrolled for prenatal care in the Jefferson County Health Department from 1985 to 1988. Our data analysis was approved by the University Institutional Board for Human Use and, because there were no specific patient identifiers, no informed consent was deemed necessary. In the above-mentioned study, 1518 women of parity one or two were screened for 11 risk factors for FGR, including hypertension, smoking, thinnness, short stature, low maternal weight and a history of a pre-term or low birth weight infant, and were entered into a prospective study of repetitive FGR. The racial designation of these women was based on self-reporting. The women participating in the project received four of their prenatal visits at a research clinic. At each of these visits they received an ultrasound examination, had blood samples collected and answered many questions about their home and work environments, social relationships, nutrition, financial and education status. In addition, standardized psychosocial scales measuring stress, mastery, trait anxiety, depression, social support and self-esteem were administered. The results of these studies have been previously reported [17]. At delivery, cord blood was obtained on most neonates. In addition to birth weight, extensive neonatal anthropometric data were collected.

Of the infants born to the original project participants, a subset was chosen for follow-up at 5 years of age. This subset of 931 children included all cases of foetal growth retardation, a control group matched to the race, gender and gestational age at delivery, all pre-term births less than 34 weeks gestational age, all twins and a 15% random sample of the original screened population. An additional 324 babies identified as growth retarded at birth, whose mothers did not participate in the prenatal project, were also included in the sample to be evaluated at 5 years.

The examination at 5 years of age collected extensive information on all aspects of home and school environment, nutrition and health history. Cognitive ability was assessed by several different instruments. Gross and fine motor skills were also evaluated, neurologic and auditory screening performed, and anthropometric measurements made. As the 5 year evaluations progressed, it was decided to add blood pressure determinations to the remaining subjects. As a result of this late decision, only 262 children who remained in the 5-year-old age window were eligible to have blood pressure determined and are the subjects of this analysis. Clinical evaluation of the children, including blood pressure measurements was performed in a quiet setting in a paediatric research clinic. Blood pressure was determined manually using a mercury sphygmomanometer and blood pressure cuffs of appropriate for the size of the child. A single blood pressure measurement was made with the child in the sitting position. The first and fifth Korotkoff sounds determined respectively systolic (SBP) and diastolic blood pressure (DBP). The population of children whose blood pressures were determined (n = 262) did not differ from the group whose blood pressures were not measured either by %FGR, %pre-term, race, birth weight or multiple births. Maternal age for the study group was slightly younger (28.9 vs 29.7 years, \( P = 0.04 \)) and the group studied included more males (57 vs 49\%, \( P = 0.035 \)).

Pre-term delivery was defined as less than 37 completed weeks of gestation. Gestational age was defined as the number of days from the first day of the last menstrual period (LMP) to delivery when that gestational age was within 2 weeks of the age based on an ultrasound examination. If there were more than a 2 week discrepancy between dates or if the woman was unsure of the LMP date, gestational age was based on the first ultrasound examination. FGR was defined as less than the 10th percentile of birth weight for gestational age according to the Brenner scale, a standard that is neither race- nor gender-specific [18]. In the Jefferson County Health Department population from which our study population was drawn, this definition resulted in \(~6\%\) of the health department population being classified as having FGR.

Statistical analysis was performed using SAS 8.2. Mean blood pressure values were compared using Student’s t-test and rates and proportions were compared using \( \chi^2 \)-squared or Fisher’s exact test where appropriate. Linear regression models were used to evaluate the effects of birth weight and body mass index (BMI) on SBP and DBP. Multivariate linear regression models were used to model the effects of FGR, the child’s BMI, race, gender, maternal smoking and gestational diabetes on SBP and DBP while adjusting for possible confounders. Interactions between race and FGR and race and BMI were tested. The interaction of race and FGR was significant and was included in the final model. A \( P \)-value of \(<0.05\) was considered to be statistically significant. Except where noted, the values represent mean ± SD.

Results

No significant differences in SBP or DBP were observed between the mothers of children who were appropriate for gestational age (AGA) or those of FGR children, nor were there significant differences in their pre-pregnancy BMI (Table 1). Gestational diabetes was present in 4\% of the mothers and was more prevalent in mothers of children whose birth weights were appropriate for gestational age when compared to those whose children had FGR (4.8 vs 1.8\%). Of these mothers, seven were African American, of whom only one was in the FGR group. There were six African American and three white mothers with gestational diabetes in the AGA group. The percentage of mothers who smoked was about the same in both groups (FGR = 46.2 vs AGA = 36.9\%). Alcohol consumption
was somewhat less prevalent in the mothers of FGR as compared with AGA children (25.0 \(\text{vs}\) 34.3\%, Table 1).

Of the 262 children, 204 had appropriate birth weights for their gestational ages (2971 \(\pm\) 675 g) (Table 2). Fifty-eight children (22\% of our study population) had a mean birth weight of 2330 \(\pm\) 407 g, and were considered to have FGR. Their mean birth weight was significantly lower than that of the AGA group \((P<0.0001, \text{Table 2}).\) No significant differences between the FGR group and the AGA groups were observed for gender distribution, gestational age and BMI, weight and height at age 5 years. While black children were more prevalent in the FGR and AGA groups, no significant differences were noted for racial distribution (Table 2). No significant differences were noted between FGR and AGA children for SBP and DBP at age 5. However, when race differences were examined within the AGA and FGR groups, white children in the FGR group had higher systolic blood pressures than did the black children (102.7 \(\pm\) 9.3 mmHg, \(n=10\) \(\text{vs}\) 92.2 \(\pm\) 11.0 mmHg, \(n=48\), \(P=0.007).\) White children also had slightly higher diastolic blood pressures (64.2 \(\pm\) 8.5 \(\text{vs}\) 58.5 \(\pm\) 9.8 mmHg) but the difference was not statistically significant.

No significant ethnic differences for either SBP or DBP were seen within the AGA group, although African American children had slightly higher systolic blood pressures (94.1 \(\pm\) 11.0 mmHg \(\text{vs}\) 91.2 \(\pm\) 9.6 mmHg, \(P=0.085).\) Of the 204 children in the AGA group, 67 children, 58 African American and 9 white were delivered pre-term. Their durations of gestation were the same (33.6 weeks for white children; 34.5 weeks for African American). Within the AGA group, there were also no differences in SBP or DBP in either of the pre-term subsets (93.2 \(\pm\) 11.3/59.3 \(\pm\) 8.8 mmHg for black and 96.6 \(\pm\) 7.4/62.6 \(\pm\) 6.3 for white children).

The relationship between birth weight and blood pressure at age 5 years was analyzed by linear regression. No significant association between systolic SBP or DBP and birth weight was found in the total group \((r=0.05, P=0.41).\) Neither was there an association with DBP \((r=0, P=0.98).\) However, SBP in white children was inversely associated with birth weight \((r=-0.295, P=0.017, \text{Figure 1A})\) such that for each kilogram decrease in birth weight there was a 5 mmHg increase in SBP. Conversely, we noted a small but significant positive association between birth weight SBP in the African American children \((r=0.15, P=0.03, \text{Figure 1A})\). Thus for every kilogram increase in their birth weight, blood pressure increased by 2 mmHg. There was no association between DBP and birth weight in either group (Figure 1B).

A similar analysis testing the relationship between gestational age and blood pressure revealed no significant relationship with either SBP or DBP for the total group or for either racial subgroup of children.

When SBP and BMI at age 5 were similarly analyzed, a strong positive association was observed in the total group \((r=0.268, P<0.0001)\) with the strongest observed in the African American children \((r=0.272, P<0.0001, \text{Figure 2A}).\) Each kg/m\(^2\) of BMI was associated with a 1.5–1.8 mmHg increase in SBP. BMI was also associated with a significantly higher DBP in the group as a whole \((r=0.183, P=0.003)\) and in African American children \((r=0.199, P=0.005, \text{Figure 2B}).\) Table 3 shows the results of multiple linear regression analyses using a model consisting of gender, gestational age, FGR (Y/N), BMI and height of child at age 5 and pre-pregnancy BMI of mother, maternal

### Table 1. Characteristics of the mothers of the 262 subject children

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total group</th>
<th>FGR</th>
<th>AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28.9±4.9 ((n=252))</td>
<td>28.7±5.6 ((n=56))</td>
<td>29.0±4.8 ((n=196))</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>109.5±14.0 ((n=250))</td>
<td>109.9±16.5 ((n=55))</td>
<td>109.4±13.3 ((n=195))</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>60.8±11.3 ((n=250))</td>
<td>61.3±13.0 ((n=55))</td>
<td>60.7±10.9 ((n=195))</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.8±5.6 ((n=197))</td>
<td>23.4±5.6 ((n=33))</td>
<td>23.8±5.6 ((n=164))</td>
</tr>
<tr>
<td>Gest. diabetes (%)</td>
<td>10 (4.27) ((n=243))</td>
<td>1 (1.9) ((n=56))</td>
<td>9 (5.0) ((n=187))</td>
</tr>
<tr>
<td>Active smoker (%)</td>
<td>97 (40.4) ((n=250))</td>
<td>24 (48.0) ((n=52))</td>
<td>73 (38.4) ((n=198))</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>80 (33.3) ((n=248))</td>
<td>13 (26.0) ((n=52))</td>
<td>67 (35.3) ((n=196))</td>
</tr>
</tbody>
</table>

Values are mean±SD or the actual number where indicated. Number per group is noted below data points. There were 252 mothers of 262 children including 10 sets of twins.

### Table 2. Characteristics of subject children at age 5 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total ((n=262))</th>
<th>FGR ((n=58))</th>
<th>AGA ((n=204))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>5.63±0.53</td>
<td>5.66±0.59</td>
<td>5.62±0.50</td>
</tr>
<tr>
<td>BWT (g)</td>
<td>2829±679</td>
<td>2330±407</td>
<td>2971±675*</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>38.1±2.6</td>
<td>38.5±2.1</td>
<td>37.9±2.8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>93.5±10.8</td>
<td>94.1±11.3</td>
<td>93.4±10.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>58.5±9.5</td>
<td>59.5±9.8</td>
<td>58.3±9.4</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>15.8±1.8</td>
<td>15.5±1.7</td>
<td>15.9±1.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>113.1±5.4</td>
<td>112.8±5.9</td>
<td>113.2±5.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.4±3.7</td>
<td>19.8±3.4</td>
<td>20.5±3.8</td>
</tr>
<tr>
<td>Female (n)</td>
<td>113</td>
<td>29</td>
<td>84</td>
</tr>
<tr>
<td>Male (n)</td>
<td>149</td>
<td>29</td>
<td>120</td>
</tr>
</tbody>
</table>

Values are mean±SD or the actual number where indicated. \(^*P<0.0001.\)
age, smoking history, maternal gestational diabetes (Y/N) and maternal SBP and DBP. Race (B/W) was included as a parameter only for the total group analysis. FGR was strongly associated with SBP in the group as a whole, accounting for a 13.2 mmHg difference between FGR and AGA groups. However, together with a smaller but significant inverse association with gestational age, these effects were only noted in white children. Gestational diabetes was strongly associated with blood pressure, accounting for an 8 mmHg increase in the total group but the effect was seen exclusively in African American children, accounting for a 10.2 mmHg difference in SBP from those not so exposed. Smoking and gender were also significantly associated with SBP but again these were only noted in the African American group. Inexplicably, in this study, maternal smoking was associated with lower SBP in African American children and higher pressure in the whites. However, active smoking was more prevalent among the white mothers (68% vs 30%, \( P < 0.0001 \)) who also smoked more heavily than African American mothers (18% vs 2% of smokers smoking more than one package of cigarettes per day, \( P = 0.0005 \)). Although univariate linear regression showed BMI to be directly associated with blood pressure in both ethnic groups, the multivariate analysis revealed only a significant positive association between BMI and SBP in African American children.
Discussion

The present findings support the view that birth weight significantly affects childhood blood pressure; however, in our study population, the effect varied according to racial classification. Multiple linear regression analysis revealed significant inverse associations between FGR and SBP and between gestational age and SBP in white children in accord with the preponderance of published data [1–3]. These findings also suggest that pre-term delivery, even in the absence of FGR, contributed to higher blood pressure in these children, supporting Lurbe et al. [19] who reported that low birth weight may be a determinant of SBP even in the absence of FGR.

We were surprised not to find such an inverse association between SBP and either FGR or gestational age in the black children since they represented the majority of our study population and since the high prevalence of low birth weight and FGR in African Americans has suggested that FGR might be an important contributor to their increased risk for hypertension and renal disease [13]. In contrast, we found a positive association between birth weight and systolic blood pressure (Figure 1) in the black children. Our failure to see an effect of FGR or gestational age on the blood pressure of these African American children differs from the findings of Yiu et al. [2] and those reported for Soweto children [14]. Nevertheless, our findings supports other reported observations. In an examination of low birth weight and blood pressure in a biracial sample of children age 7–11 years, Donker et al. [9] found that low birth weight was associated with higher blood pressure in African American boys but the association was lost when multivariate analyses were done. Similarly, Falkner and colleagues [7,10] failed to find an inverse association between birth weight and blood pressure in young black adults, and a study of blood pressure in Nigerian children similarly failed to demonstrate an inverse association between birth weight and blood pressure [15]. The explanation for these discrepant observations is not clear.

One factor that may minimize the role of low birth weight is the BMI of the subjects at the time blood pressure was measured. Many studies have found that, irrespective of racial designation, BMI was statistically more strongly associated with blood pressure in both children and adults [6–11], masking any association of low birth weight with blood pressure. Such observations suggest that the combination of BMI and low birth weight, rather than low birth weight alone contribute to higher blood pressure, perhaps through increased rates of growth [11,16,20,21]. Our univariate analyses support this view demonstrating that SBP was more strongly associated with BMI than with birth weight. Nevertheless, BMI did not negate the strong association between FGR and SBP in the total group of children, suggesting that both factors may play a role in determining blood pressure at age 5 in these children.

We also found a strong association between gestational diabetes and level of systolic blood pressure (Table 3), in accord with observations that maternal glycaemia is linked to higher neonatal blood pressure [22]. In our study, the effect of gestational diabetes was greatest in African American children in whom it contributed 10 mmHg to systolic blood pressure. Our data suggest that in African American children, gestational diabetes, increased birth weight and increased BMI are associated with higher blood pressure and, in part, support the findings of Hoy et al. [3] who reported a positive correlation between higher birth weight, BMI, blood pressure and rates of diabetes mellitus in Australian Aborigines. While one might speculate that the association we found contributes to the high prevalence of hypertension and non-insulin dependent diabetes mellitus in African Americans, our data do not allow us to draw such a conclusion. Moreover, the low prevalence of gestational diabetes in this study may overestimate its relative effect on childhood blood pressure. Nevertheless the above finding certainly support the view that maternal factors affecting the intrauterine environment influence childhood blood pressure.

Our data also suggest that FGR may not be required for increased susceptibility for hypertension or kidney disease later in life. In this regard, Fan et al. [23] found only 13% of blacks and 7.5% of whites with stage 5 chronic kidney disease in South Carolina had low birth weight and Hoy et al. [3] found low birth weight associated with overt albuminuria in only 27% of African American children. Moreover, the prevalence of hypertension in blacks in the United States is 34% while the prevalence of low birth weight in this population is only ~11% [12].

We have no explanation for the disparate effects of birth weight, FGR and gestational age on blood pressure in white and African American children seen in this study. Perhaps had the number of subjects in the two groups been larger, inter-group differences would have been less obvious. In this regard, the small number of white children in the FGR group may have been a non-representative sample. A larger number might have yielded different results. Nevertheless, our observations in this very small sample are in accord with many of the previously cited studies. Alternatively, it may be that, despite the greater representation of black children in the FGR group and despite their increased risk for low birth weight, the occurrence of risk factors, such as maternal smoking, increased foetal blood glucose concentration resulting from gestational diabetes, and/or the effects of BMI may have masked or minimized any effect of FGR. Moreover, the effects of other potential intrauterine and post-delivery factors, not examined here, may also have minimized any potential contribution of low birth weight and early gestational age to increased blood pressure. Lastly, it is possible that the effects of
FGR on blood pressure appear later in African Americans.

In summary, we found that the effects of birth weight on blood pressure may vary depending on the racial designation of the groups studied. We found no association between FGR or gestational age and SBP in African American children, age 5 years, while such an association was observed in the white children. In African American children SBP was directly associated with birth weight and maternal gestational diabetes and inversely with maternal smoking. The BMI of the both groups of children at age 5 years was directly associated with systolic blood pressure. The relative importance of these effects on blood pressure may depend on other prenatal and post-partum risk factors. Our data do not allow us to determine whether any of the risk factors examined in this study portend future hypertension and/or renal disease.

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Conflict of interest statement. None declared.

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