The association between intrauterine growth restriction in the full-term infant and high blood pressure at age 7 years: results from the Collaborative Perinatal Project

Anusha H Hemachandra,1,2* Mark A Klebanoff,2 Anne K Duggan,3,4 Janet B Hardy4 and Susan L Furth5,6

Accepted 30 March 2006

Objective To use neonatal and placental anthropometry as proxy measures of intrauterine growth restriction (IUGR) and to relate these to blood pressure later in childhood.

Study design A post hoc analysis of full-term white and black children from the Collaborative Perinatal Project, followed from birth until age 7 years (n = 29 710). Blood pressure above the 90th percentile by gender and race was considered high blood pressure. Anthropometric measures at birth included birth weight, ponderal index (PI, birth weight/birth length3), head to chest circumference (HCC) ratio, and placental ratio percentage (PRP, placental weight*100/birth weight).

Results Among anthropometric measures, PI, HCC, and birth weight were not associated with high systolic blood pressure at age 7 years, but PRP was. In multiple logistic regression, high systolic blood pressure and widened pulse pressure were both predicted by increased PRP [odds ratio (OR) 1.03 and 1.04, \( P < 0.001 \)] but not by birth weight, when adjusted for gender, race, and maternal education. High diastolic blood pressure was weakly predicted by birth weight (OR 1.10, \( P = 0.05 \)) but not by PRP.

Conclusions PRP is associated with an increased risk for high systolic blood pressure and pulse pressure later in childhood, whereas birth weight, PI, and HCC are not. The proportion of placental weight to birth weight is a useful marker of IUGR for studying the developmental origins of adult disease hypothesis.

Keywords Hypertension, fetal programming, placenta, anthropometry, neonatal

---

1 Division of Neonatology, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.
2 Division of Epidemiology, Statistics, and Prevention Research, Department of Health and Human Services, National Institutes of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA.
3 Department of Health Policy and Management, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA.
4 Division of General Pediatrics, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.
5 Division of Pediatric Nephrology, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.
6 The Welch Center for Prevention, Epidemiology, and Clinical Research, The Johns Hopkins Medical Institutions, Baltimore, MD, USA.

* Corresponding author. DESPR/NICHD/NIH, 6100 Building, Room 7B05, MSC 7510, Bethesda, MD 20892, USA. E-mail: hemachaa@mail.nih.gov

Low birth weight, as an indicator of fetal growth restriction (FGR), has recently been associated with a number of chronic diseases in adult life. First widely publicized by David Barker1 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.2 The hypothesized consequence is that growth-restricted neonates develop into children and adults with an increased risk for chronic diseases such cardiovascular disease,3 type II diabetes,4 metabolic syndrome,5 and

---
osteoporosis. The body of evidence from epidemiological studies is controversial owing to potential random error effects and the inappropriate adjustment for confounding factors. Additionally, most of these studies are limited by the use of low birth weight (<2500 g) as the definition of FGR. FGR has been defined as a reduction in the expected pattern of fetal growth resulting from processes that inhibit the growth potential of the fetus. By this definition, the slowing of growth during any period of gestation would indicate FGR, however this does not necessarily result in low birth weight. There may be individuals who have underlying FGR, despite weighing >2500 g. Thus, birth weight is an inconsistent marker of FGR and may not be optimal for studying the ‘fetal programming’ hypothesis.

Anthropometric measures other than birth weight may be more sensitive indicators of FGR. These include ponderal index (PI), head to chest circumference (HCC) ratio, and placental ratio. PI, a measure of ‘thinness at birth,’ is the most commonly used indicator of body proportion in the neonate. It has been associated with FGR and also associated with health outcomes later in life such as cardiovascular disease and non-insulin dependent diabetes. HCC ratio is an indication of symmetric or asymmetric growth restriction, with implications for head-sparing and visceral organ growth in utero. Placental ratio, or the ratio between the weight of the infant and the weight of the placenta, is also considered to be an alternative indicator of FGR. It has been studied in association with FGR, maternal anaemia, gestational diabetes, and hypertension later in life. These measures may be more appropriate than birth weight for detection of FGR when examining the ‘fetal programming’ hypothesis.

We hypothesize that the use of neonatal and placental anthropometric measurements instead of birth weight alone to assess FGR would strengthen the observed relationship between FGR and blood pressure later in life. To examine the relationship between several proxy measures of FGR and blood pressure in childhood, we used data from one of the largest prospective studies of women and children in the US, the Collaborative Perinatal Project (CPP).

Methods

The CPP enrolled pregnant women at 12 academic medical centres in the US in a nationwide cohort between 1959 and 1965. Women were enrolled at their first prenatal visit and were followed during pregnancy, labour, and delivery. At the time of delivery, a trained observer was present to collect data on the newborn, including anthropometric measurements and placental weight. Of note, the placentae were trimmed of membranes and cord as per study protocol prior to measurement. The offspring were followed for 7 years, with multiple questionnaires regarding medical and social history, detailed neuropsychological testing, and physical examinations at 4 months, 8 months, 1 year, 3 years, 4 years, and 7 years of age. The blood pressure measurement at age 7 years was taken once with a manual sphygmomanometer on the right arm of the child in a sitting position, prior to the physical exam and phlebotomy. Comprehensive descriptions of the methodology of the study have been published previously. High blood pressure was defined as blood pressure/pulse pressure above the 90th percentile within the NCPP population blood pressure distributions by gender and race. The data are currently available for public use with patient identifiers omitted from the dataset.

The hypothesis and anthropometric measures of interest for this retrospective analysis were identified a priori. Of the 58960 pregnancies enrolled in the study, 51 540 mothers of white or black race were identified and were eligible for this analysis. The remainder were identified as ‘Hispanic’, ‘Asian’, or ‘other’, and comprised such a small proportion of the total population that they were excluded to allow meaningful race-specific blood pressure distributions. After excluding stillbirths, terminations, premature births, and women who dropped out of the study prior to delivery, 41 413 infants were born between 37 and 42 completed weeks estimated gestational age by menstrual dating. From this group, there were 417 known deaths from birth to age 7 years, further restricting the pool of eligible subjects to 40 996. Of these babies, 29 973 completed the follow-up until 7 years of age (73%). These subjects were included in this analysis.

In addition, exclusion criteria were applied to remove biologically implausible data from the analysis. The data inspected for possible exclusion included birth weight, head circumference, chest circumference, birth length, placental weight, and systolic and diastolic blood pressure at age 7 years, and weight and height at age 7 years. Using Tukey’s Severe Outlier Criteria, as well as excluding data points 4 or more standard deviations from the mean, 154 subjects were removed from the analysis. A total of 109 children diagnosed with heart or kidney disease of any kind were also excluded. The final study population included in this analysis numbered 29 710 subjects.

The anthropometric measures of interest were defined as follows: Placental ratio percentage (PRP) was defined as the placental weight in kilograms divided by the birth weight in kilograms, multiplied by 100 to give the ‘percentage’ of birth weight comparable with the weight of the placenta. Therefore, an infant with relatively low birth weight in relation to placental weight would have a high PRP. PI was defined as the birth weight in grams divided by the length in centimetres cubed, multiplied by 100. HCC ratio was defined as the head circumference in centimetres divided by the chest circumference in centimetres. Small for gestational age (SGA) infants were defined by a birth weight less than the 10th percentile for gender, race, and gestational age using birth weight distributions within this study population.

Bivariate analyses implemented Student’s t-tests and Chi-square tests where appropriate. We also constructed multivariable logistic regression models to predict the presence of high systolic, diastolic, and pulse pressures at age 7 years in this cohort, using suspected risk factors for childhood hypertension. Forward stepwise logistic regression technique was used, with an entry criterion of P < 0.05 and a removal criterion of P > 0.10. These risk factors include maternal education, race, and gender, as well as birth weight and PRP. Gender was included in the model with the expectation that boys would have higher blood pressure at 7 years than girls. PRP was included in the model because of the statistically significant association between PRP and blood pressure in...
univariate analysis. All statistical analysis was performed using SPSS version 11.0 software (Chicago, 2003).

Results

The women included in this analysis were relatively young and thin, with a mean age of 24.5 years (SD 6.1 years) and a mean pre-pregnancy body mass index of 22.9 (SD 4.3). Almost half of this population smoked during pregnancy (46.7%). The rates of pregnancy complications, such as pre-eclampsia (2.5%), and pregnancy-induced hypertension (0.7%), and pregnancy-induced diabetes (0.7%), and pregnancy-induced hypertension (0.7%), and pregnancy-induced diabetes (0.7%), and pregnancy-induced hypertension (0.7%), and pregnancy-induced diabetes (0.7%) in this population were lower than current norms in the US.24–26 Approximately 15% of women of pregnancy complications, such as pre-eclampsia (2.5%), and pregnancy-induced hypertension (0.7%), and pregnancy-induced diabetes (0.7%) in this population were lower than current norms in the US.24–26 Approximately 15% of women enrolled in the CPP study were below the poverty level, based on US Census Bureau standards for family income from 1960–70, and these mothers had a mean education level of 10.6 ± 2.6 years.

The children born into this CPP subpopulation are characterized in Table 1. The population was almost evenly distributed among white and black infants, with no discernable difference in length of gestation (39.9 and 39.5 weeks, respectively). White infants had a higher mean birth weight than black infants (3.32 and 3.14 kg) as well as a higher mean placental weight than black infants (450 and 432 g). They also had significantly higher mean systolic and diastolic blood pressures than the black infants at the 7 year follow-up. However, pulse pressure was comparable across racial groups (40.9 mm Hg for white infants and 40.8 mm Hg for black infants).

In Table 2, the anthropometric measurements of SGA infants are compared with their appropriate for gestational age counterparts (birth weight above the 10th percentile for gender and race). SGA infants had significantly lower birth weight, birth length, placental weight, head circumference, and chest circumference when compared with AGA infants in this population. SGA infants also had a significantly higher PRP than their appropriately grown counterparts (14.4 ± 2.9% compared with 13.6 ± 2.3%, P < 0.001). For HCC ratio there were no significant differences between the two groups, and for PI there was a lower mean index in the SGA group, but this was not statistically significant.

Anthropometric measurements were compared between children with high blood pressure or widened pulse pressure and their normal counterparts at age 7 years. Subjects with SBP, DBP, or PP above the 90th percentile by gender and race within the CPP population were compared with those having SBP, DBP, or PP below the 90th percentile (Table 3). There were no significant differences in mean birth weight between children with high SBP or DBP and those with normal blood pressure. Children with high systolic blood pressure had a statistically significant higher mean PRP than did normotensive children in this population (13.8 and 13.6%, respectively, P < 0.001), but there were no significant differences in PI and HCC ratio between the two groups. Children with high diastolic blood pressure had no statistically significant differences in PRP, PI, or HCC ratio from children with normal diastolic blood pressure. Children with a widened pulse pressure had a significantly higher mean PRP (13.9 and 13.6%, P < 0.001) and a lower mean PI (2.55 vs 2.57, P < 0.001) than did their counterparts. However, there were no significant differences between the two groups in birth weight or HCC ratio.

In Table 4, trends in the prevalence of high SBP among the various birth weight and PRP categories controlling for birth weight are demonstrated. The 4859 infants without a recorded placental weight are not included in this table. Within each birth weight group (birth weight <2500 g, birth weight 2500–4000 g, and birth weight >4000 g), a higher PRP is associated with a higher prevalence of high systolic blood pressure. This trend is consistent across all three birth weight categories and is statistically significant at the P < 0.01 level. Overall, an increasing trend in prevalence of high blood pressure is evident as PRP increases, regardless of birth weight category, and this trend is also statistically significant at the P < 0.01 level. Within the first two PRP categories, as birth weight group increases, the prevalence of high blood pressure remains relatively constant. In the highest PRP category, the prevalence of high blood pressure decreases as birth weight increases (P < 0.01).

Table 5 displays the association of birth weight and PRP with blood pressure at age 7 years, with and without adjustment for covariates. As in univariate analysis, birth weight is not a significant predictor of high systolic blood pressure in multivariable analysis (unadjusted odds ratio
As with the previously cited study, birth weight was a weak predictor of elevated diastolic blood pressure, with every percentage increase in PRP increasing the likelihood of high SBP at age 7 by almost 3% (OR = 1.03, 95% CI 1.00–1.05). The strongest predictors of high systolic blood pressure were maternal education, race, and gender entered into the model, regardless of whether or not potential confounders were adjusted for in the model (OR = 1.04, 95% CI 1.02–1.06). As was true for elevated systolic and diastolic blood pressure, widened pulse pressure was predicted by maternal education.

### Table 3 Infant anthropometric measurements by high blood pressure at age 7 years

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Children with high SBP</th>
<th>Children with normal SBP</th>
<th>Children with high DBP</th>
<th>Children with normal DBP</th>
<th>Children with wide PP</th>
<th>Children with normal PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>3.24 (0.47)</td>
<td>3.23 (0.48)</td>
<td>3.26 (0.48)</td>
<td>3.23 (0.48)</td>
<td>3.24 (0.48)</td>
<td>3.24 (0.48)</td>
</tr>
<tr>
<td>Placental percentage</td>
<td>13.8 (2.3)</td>
<td>13.6 (2.3)</td>
<td>13.3 (2.3)</td>
<td>13.3 (2.3)</td>
<td>13.9 (2.4)</td>
<td>13.6 (2.3)</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>2.57 (0.35)</td>
<td>2.57 (0.50)</td>
<td>2.57 (0.35)</td>
<td>2.57 (0.50)</td>
<td>2.55 (0.38)**</td>
<td>2.57 (0.50)</td>
</tr>
<tr>
<td>HCC ratio</td>
<td>1.06 (0.50)</td>
<td>1.06 (0.50)</td>
<td>1.06 (0.50)</td>
<td>1.05 (0.50)</td>
<td>1.06 (0.50)</td>
<td>1.06 (0.50)</td>
</tr>
</tbody>
</table>

Table 4 Prevalence of high systolic blood pressure by birth weight and placental percentage*

<table>
<thead>
<tr>
<th>Placental ratio percentage</th>
<th>Birth weight 1077–2500 g (n = 1383)*</th>
<th>Birth weight 2501–4000 g (n = 22 008)*</th>
<th>Birth weight 4001–5386 g (n = 1460)*</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9–12.4 (n = 8223)</td>
<td>9.2 (9.3)</td>
<td>9.3 (9.3)</td>
<td>9.3 (9.3)</td>
<td></td>
</tr>
<tr>
<td>12.5–14.3 (n = 8361)</td>
<td>10.5 (10.3)</td>
<td>10.1 (10.3)</td>
<td>10.1 (10.1)</td>
<td></td>
</tr>
<tr>
<td>14.4–15.0 (n = 8267)</td>
<td>13.3 (12.0)</td>
<td>11.8 (12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>11.6 (10.5)</td>
<td>10.3 (10.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.01 for chi-square comparisons of percentage of high SBP by PRP within each birth weight group.

### Table 5 Multivariable model of the relationships between risk variables measured in childhood and high blood pressure at age 7 years

<table>
<thead>
<tr>
<th>Risk variable</th>
<th>Unadjusted Odds Ratio 95% CI</th>
<th>Adjusted Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dependent variable: high systolic blood pressure</strong>&lt;sup&gt;a&lt;/sup&gt; at age 7 years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>0.95 (0.88–1.02)</td>
<td>1.05 (0.96–1.15)</td>
</tr>
<tr>
<td>PRP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.03 (1.01–1.05)</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td>1.05 (1.03–1.06)</td>
<td>0.94 (0.93–0.96)</td>
</tr>
<tr>
<td>Black race</td>
<td>1.35 (1.25–1.45)</td>
<td>1.42 (1.30–1.54)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.96 (0.89–1.03)</td>
<td>0.95 (0.88–1.03)</td>
</tr>
<tr>
<td><strong>Dependent variable: high diastolic blood pressure</strong>&lt;sup&gt;b&lt;/sup&gt; at age 7 years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>0.90 (0.83–0.97)</td>
<td>1.10 (1.00–1.20)</td>
</tr>
<tr>
<td>PRP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.01 (0.99–1.03)</td>
<td>1.01 (1.00–1.03)</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td>1.02 (1.00–1.04)</td>
<td>0.98 (0.96–0.99)</td>
</tr>
<tr>
<td>Black race</td>
<td>1.25 (1.16–1.35)</td>
<td>1.20 (1.10–1.31)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.99 (0.91–1.07)</td>
<td>0.94 (0.87–1.02)</td>
</tr>
<tr>
<td><strong>Dependent variable: widened pulse pressure</strong>&lt;sup&gt;b&lt;/sup&gt; at age 7 years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>1.05 (0.97–1.14)</td>
<td>0.94 (0.85–1.03)</td>
</tr>
<tr>
<td>PRP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.04 (1.02–1.06)</td>
<td>1.04 (1.02–1.06)</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td>1.04 (1.02–1.05)</td>
<td>0.95 (0.93–0.97)</td>
</tr>
<tr>
<td>Black race</td>
<td>1.34 (1.24–1.45)</td>
<td>1.48 (1.35–1.62)</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.08 (1.00–1.17)</td>
<td>1.09 (1.00–1.19)</td>
</tr>
</tbody>
</table>

* Forward stepwise logistic regression with birth weight, placental ratio, percentage, maternal education, race, and gender entered into the model.

** Defined as blood pressure/pulse pressure above the 90th percentile within blood pressure/pulse pressure distributions within the NCPP population blood pressure distributions by gender and race.

<sup>a</sup> Placental ratio percentage: calculated as the placental weight in kilograms divided by the cube of length in metres.
but the direction of the association depended upon adjustment for confounders (unadjusted OR = 1.04, 95% CI 1.02–1.05; adjusted OR = 0.95, 95% CI 0.93–0.97). Female gender and black race were also significant positive predictors, regardless of adjustment for confounders.

Discussion

This study of the association between anthropometric measurements at birth and blood pressure at age 7 years detected statistically significant relationships between PRP and both high systolic blood pressure and widened pulse pressure. PI and HCC ratio were not statistically significant predictors of high blood pressure. Birth weight was of borderline significance in the prediction of diastolic blood pressure at age 7 years in multivariable analysis and was not significant in univariate analysis.

Given the time period when these data were collected (1960s and 1970s), blood pressures were measured by a manual sphygmomanometer and systolic pressure was most likely more accurately measured than diastolic pressure owing to the difficulty in hearing the muffling of the fourth Korotkoff sound. Thus, either the possible introduction of error into the diastolic blood pressure data collection or the aetiology of the causal pathway itself may explain the lack of association of diastolic blood pressure with birth indices. It is not surprising that the regression model for the prediction of SBP in this population somewhat mirrors the model for the prediction of PP, because in adult populations, both systolic blood pressure and pulse pressure have been shown to be strong indicators of arterial stiffness. Decreased arterial distensibility, caused by disrupted elastin deposition in the great vessels, is one of the potential pathways for FGR to ‘program’ blood pressure in post-natal life, and this may explain why both systolic blood pressure and pulse pressure are associated with a measure of FGR.

The utility of a marker of FGR that can be measured at birth, rather than prospectively during pregnancy, is clear. Birth weight has been the most easily accessible indicator of FGR, and therefore has been the most commonly reported in studies of the fetal origins hypothesis. But using low birth weight as a proxy measure of FGR has three serious limitations: it does not allow for variability in the genetic potential for growth, it does not recognize that infants in the appropriate or even large for gestational age groups can also suffer poor intrauterine perfusion or undernutrition and may be growth restricted in utero, and it cannot quantify the severity of growth restriction. This leads us to consider other possible markers of FGR that could be collected at the time of delivery, such as the three anthropometric measures we examined in this study: placental ratio, PI, and HCC ratio. Neither PI, a measure of ‘thinness’ at birth, or HCC ratio, a measure of ‘symmetry’ at birth, demonstrated any association with blood pressure later in childhood. Placental ratio, however, had a strong predictive value and may be the most useful of the anthropometric birth measurements to use when studying the fetal origins of chronic disease later in life.

The use of placental to birth weight ratio has been sporadic in the literature and is not yet widely recognized as an indication of intrauterine growth restriction (IUGR). In 1993, Barker et al. suggested that infants with a birth weight that is low relative to what would have been expected from the placental weight may be those fetuses who had not achieved their full growth potential. Both animal studies and human studies support this hypothesis. A high placental ratio has been associated with specific causes of FGR, such as smoking and maternal anaemia. We used the ‘placental ratio percentage’ to facilitate understanding the concept of the increasing size of the placenta in relation to the size of the infant as a risk factor for high blood pressure. Infants with a higher percentage had either a larger placenta than expected for the birth weight or a smaller birth weight for the placental size. Both of these scenarios are abnormal and suggest FGR. Of note, among those infants in the top tertile of PRP in this population, a lower birth weight increased the prevalence of high blood pressure at age 7 years, demonstrating that those infants with the lowest birth weight and the highest PRP are at highest risk for high blood pressure. This reinforces the concept that FGR, measured by PRP, is a risk factor for the development of hypertension later in life.

The sample size of this analysis is 50% of the original CPP population. Through exclusions of preterm infants, non-white and non-black infants, children with congenital anomalies, deaths, and a handful of infants with severely outlying data, 30% of the population was eliminated from this analysis. The remaining 20% of the original population was dropped because of non-completion of the 7 year follow-up (n = 11 023). This is a significant segment of the population however, it reflects an appropriate follow-up rate (73%) for a national multi-centre prospective study of pregnant women and children. We doubt that the loss to follow-up, which occurred in the CPP study has introduced bias into our analysis because it is unlikely that loss to follow-up occurred differentially by both high blood pressure at age 7 years (outcome) and intrauterine growth restriction (exposure). That is to say, children with high blood pressure and IUGR were probably not more/less likely to be lost to follow-up than children with high blood pressure and no IUGR.

Despite the loss to 7 year follow-up, our sample size is still extremely large and dwarfs most other published studies of the fetal origins hypothesis based on American data. To our knowledge, it is the largest analysis of the relationship between birth size and blood pressure in children in the US. The size of this study population presents both advantages and caveats for data analysis and interpretation. To determine the relationships between variables with relatively low frequencies, such as intrauterine growth restriction in term infants and high blood pressure in childhood (both with an expected prevalence of 10% in this population), a large sample size is required. Thus, the prospectively collected CPP data are particularly useful to study these relationships. However, the large sample size also means that associations of little practical importance may be statistically significant.

A controversial issue in statistical analysis of these data is the ‘reversal paradox’ for the fetal origins hypothesis. The reversal paradox, first published by Yule in 1903 and Simpson in 1951, refers to the phenomenon of the direction of the relationship between two variables being reversed when a third variable is introduced. In specific reference to the Barker hypothesis, Paneth et al. first suggested that current body
mass index at the time of a blood pressure measurement might ‘overcontrol’ when added to the relationship between birth weight and disease risk later in life. The controversy is the position of current body weight in the causal pathway of the fetal origins hypothesis. Some investigators have argued that it is not appropriate to include current body weight in a regression model for the fetal origins of hypertension, because current body weight and lifetime weight gain are in the causal pathway from birth weight to subsequent blood pressure. We withheld body mass index and weight at age 7 years from our regression model for this reason and found that birth weight was positively but statistically insignificantly related to systolic blood pressure at age 7 years. This finding is similar to other published analyses. We also examined a regression model with weight gain and body mass index at 7 years and found that the inclusion of body mass index at age 7 years in a logistic regression model to predict high systolic blood pressure caused the relationship between birth weight and blood pressure to invert and become statistically significant. This is consistent with other such models in the literature. Of note, the positive relationship between PRP and blood pressure was maintained whether or not body mass index at age 7 years was included in the model. This suggests that PRP is not on the causal pathway of high blood pressure and is, therefore, a more robust indicator of FGR than birth weight.

Our regression model predicts that every 3% increase in PRP increases the risk of high blood pressure at age 7 by 1%. While this is certainly a modest increase for an individual, it is a meaningful increase on a population level. Because blood pressure tends to track throughout the life course, a very small increase in risk at age 7 years may be amplified in middle and older age. And over the entire population, a small increase in mean blood pressure can result in millions of lives affected by cardiovascular disease. These data suggest that risk for the development of hypertension later in life can be suggested by anthropometric measurements taken as early as in the delivery room. As we gain a deeper understanding of the causal pathway between FGR and hypertension, we can begin to develop childhood interventions to counter the cardiovascular disease epidemic in adults on both an individual and a population level.

Acknowledgements

Drs A.H.H. and M.A.K. are supported by the intramural research program of the National Institute of Child Health and Human Development, National Institutes of Health. Dr A.K.D. is supported by the National Institute of Mental Health (1R03MH070333-01A1). Dr S.L.F. is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (U01DK66174).

KEY MESSAGES

- The proportion of placental weight to birth weight can be used as a marker of intrauterine growth restriction.
- This marker suggests that intrauterine growth restriction is associated with high blood pressure and widened pulse pressure in childhood.

References

we go from here?

Commentary: Early life determinants of blood pressure in childhood—where do we go from here?

Peter H Whincup and Christopher G Owen

An important component of the evidence suggesting that cardiovascular disease has its origins in early life, possibly influenced by poor fetal nutrition, is provided by the studies (now more than a hundred in all) that have reported on the