Indicators of Fetal Growth Do Not Independently Predict Blood Pressure in 8-Year-Old Australians

A Prospective Cohort Study

Valerie Burke, Lawrie J. Beilin, Kevin V. Blake, Dorota Doherty, Garth E. Kendall, John P. Newnham, Louis I. Landau, Fiona J. Stanley

Abstract—Inverse associations between size at birth and blood pressure (BP) in later life are commonly statistically significant only after adjustment for current size, consistent with change in size as the determinant. Few studies have been prospective or have included a range of potential confounders. Using regression models, including maternal and demographic variables, we examined associations between size at birth and BP in Australian children followed from week 16 of gestation to the age of 8 years. BP measurements were available from 1417 children born after 37 weeks gestation without congenital abnormalities. In models adjusted only for sex, the birthweight (BW), birth length, ponderal index, head circumference, chest circumference, abdominal girth, mid-arm circumference, triceps skinfold, placental weight, or BW/placental weight ratio did not significantly predict SBP in 8-year-olds. With adjustment for current size, associations were inverse but not statistically significant (regression coefficients: BW, −1.11; 95% confidence limits [CL], −2.22, 0.01; birth length, −0.25; 95% CL, −0.52, 0.24) and remained nonsignificant after adjustment for confounders. Current weight, height, or body mass index significantly predicted SBP and DBP (P<0.001) with differences of 8/4 mm Hg between upper and lower quartiles; effects were similar in infants with lower and higher BW. These findings are consistent with postnatal change in size as the major determinant of BP in 8-year-olds and are important in the context of the worldwide “epidemic” of obesity in childhood as a likely precursor of increasing rates of hypertension in adults. (Hypertension. 2004;43:1-6.)

Key Words: blood pressure • children

Inverse associations between fetal growth and disease in later life provided the basis for the original “fetal origins” hypothesis.1 Programming in utero, arising from triggers that may include fetal undernutrition, is proposed to lead to permanent changes in structure or function in organ systems.2 Lower birthweight (BW) has been examined as a predictor of higher blood pressure (BP) in children and adults and is considered in meta-analysis,3– 6 but most reported results have been adjusted for current size.

According to Lucas et al.,7 current weight adjusted for BW measures postnatal change in weight, and appropriate models should therefore include as independent variables: early size, early and later size, early and later size and interaction between these variables, and later size alone. Support for the fetal origins hypothesis, as it relates to associations between size at birth and BP, then requires a significant negative relationship between BW and outcome in the early size model, possibly augmented in the early and later size model; any interaction should be negative.

In their meta-analysis, Huxley et al.8 also noted problems associated with inappropriate adjustment for current weight. They also considered the effects of publication bias, with reporting of larger effects from smaller studies, measurement error, and failure to adjust for confounders. After accounting for publication bias and the effect of adjustment for current weight, these authors estimated a reduction of only 0.4 mm Hg in SBP/kg BW and suggested that the size of the effect may be reduced further by consideration of confounders. Schluchter6 also reported that publication bias affects the association between BW and BP and found that in fixed effects models, a 1-kg increase in BW predicted SBP lower by 0.7 mm Hg in contrast to previously reported estimates of 2 to 4 mm Hg/kg increase in BW.4

The present study used data from the Western Australian Pregnancy Cohort (Raine) Study, a longitudinal study of children in Perth, Western Australia. All neonatal measurements and a range of maternal characteristics were recorded prospectively. BP at age 8 years was examined with reference
to the models advocated by Lucas et al.7 and with adjustment for confounders related to maternal health and demographic variables.

Methods
The Raine Study began in 1989 with enrollment, between 16 and 18 weeks of gestation, of 2900 women attending the King Edward Memorial Hospital in Perth, Western Australia, as reported previously.8 All mothers gave written informed consent and the study was approved by the institutional ethics committees. Information collected by midwives included placental weight, BW, birth length, head circumference, chest and abdominal circumference, mid-arm circumference, and triceps skinfold. Children were resurveyed at ages 1, 3, 6, and 8 years. Weight was measured to the nearest 500 g using Wedderburn Digital Chair Scales, with children wearing only underclothes. Height was measured to the nearest 0.1 cm with a Holtain Stadiometer. Forty-five minutes after entering the room, the child had BP measured while seated, using the appropriate cuff size9 with an oscillometric method (Dinamap 8100; Critikon). Two readings were taken 1 minute apart, and the average was used in analysis.

After exclusion of multiple pregnancies, congenital abnormalities, and children born before 37 weeks of gestation, the present analysis included 1417 children in whom BP was measured at age 8 years.

Statistical Methods
SPSS 11.0 (SPSS, Chicago, Ill) was used to produce descriptive statistics (mean and SD for continuous variables). Regression analysis was used for modeling with SBP or DBP as dependent variables. Initial models were adjusted only for sex; the second series of models was adjusted for sex and current size; the third included interaction terms (current size×neonatal measurement). Final models added adjustment for demographic and maternal characteristics. Results were considered significant if P < 0.05.

Results
The characteristics of the children at birth and at age 8 years and of the mothers of the 1417 mother–child pairs included in the analysis are shown in Table 1 and Table 2. At birth, the length, weight, chest and abdominal circumferences, and BW/placental weight ratio were all significantly greater in boys. At age 8 years, boys were significantly taller than girls, but there were no significant differences in weight, body mass index (BMI), SBP, or DBP.

Associations Between Neonatal Measurements and BP in 8-Year-Olds
Figure 1 shows SBP and DBP in 8-year-olds with reference to quartiles of BW, head circumference, birth length, and quartiles of weight. There was no significant trend across BP for quartiles of any of the variables measured at birth, but there was a significant trend for quartiles of weight at age 8 years for SBP and DBP (P < 0.001 for both variables). The results were identical if quartiles of BMI at age 8 years were used instead of quartiles of weight.

Because of significant differences in measures of size at birth between boys and girls, models were adjusted for sex. Regression coefficients relating measurements at birth of length, weight, head circumference, chest circumference, abdominal girth, mid-arm circumference, triceps skinfold, ponderal index, placental weight, and BW/placental weight ratio to SBP, adjusted only for sex, are shown in Table 3. None of these variables significantly predicted SBP, nor were they significant after additional adjustment for current weight or height (Table 3). The regression estimates indicate a decrease of 1.1 mm Hg in SBP per 1-kg increase in BW in the model adjusted for current weight and sex. An increase of 1 cm in birth length predicts a decrease of 0.2 mm Hg in SBP at age 8 years. There were no significant associations between DBP and any of the neonatal measurements, with or without adjustment for current size (data not shown).

Associations between BW and SBP were examined in the additional models proposed by Lucas et al.7 Interaction terms were included and, although negative in sign, were not statistically significant in models that examined BW or birth length. As shown in Figure 2, the effect of weight gain on BP at age 8 years is similar whether BW is in the lowest or the highest quartile, consistent with the nonsignificant interaction term in that model. That is, there is no evidence of a greater effect of weight gain in children with lower BW. In the later models, including only current size, adjusted for sex, an increase of 1 kg in current weight predicted an increase of 0.5 mm Hg in SBP, and a 1-cm increase in height predicted an increase of 0.3 mm Hg in SBP.

Adjustment for Confounders
Multivariable models were adjusted for the following variables: sex, gestational age, parity (first child or not), ethnicity (white or non-white), maternal age, change in maternal weight before pregnancy to the time of the survey of 8-year-olds, maternal BP at the time of that survey, maternal education (tertiary, secondary, other), income (3 groups), maternal diabetes, gestational diabetes, hypertension during pregnancy, antepartum hemoglobin, and maternal smoking during pregnancy (current, ex-smokers, never smokers).

Smoking status at 18 weeks was used to classify smoking habits, because 95% of mothers who smoked at that stage continued to smoke at 34 weeks. Only those variables for
which coefficients yielded probability values less than 0.10 in models adjusted for current size were examined in these multivariable models. As shown in Table 4, neither BW nor birth length significantly predicted SBP after adjustment for these potential confounders.

**Adjustment for BMI**

A second series of models used adjustment for BMI at age 8 years instead of adjustment for height or weight to avoid multicollinearity arising from simultaneous adjustment for these variables. None of these models showed significant relationships with SBP in 8-year-olds. For birth length, the regression coefficient (b) was \(-0.01\) (95% CL: \(-0.26, 0.24\); \(P=0.927\); adjusted \(R^2=0.083\)); for BW, the coefficient was \(-0.496\) (95% CL: \(-1.60, 0.61\); \(P=0.378\); adjusted \(R^2=0.089\)).

**Discussion**

This large prospective study has shown no statistically significant associations between measures of size at birth and SBP in 8-year-olds. In models adjusted only for sex, regression coefficients were not statistically significant and were positive. With adjustment for current size, the relationships became inverse but remained nonsignificant. Although signs of interaction terms for measures of size at birth and at age 8 years were negative (in the expected direction if lower BP was associated with higher birth size), these terms were also not statistically significant. The findings at age 8 years do not fulfil the criteria proposed by Lucas et al\(^7\) to be necessary for supporting the hypothesis of an association between size at birth and BP in later life. Models predicting SBP in 8-year-olds were dominated by the effects of current size, similar to other reports.\(^{10,11}\)

Publication bias, with reporting of stronger associations from smaller studies,\(^8\) may affect the estimated relationship
were adjusted for current size, showed publication bias as great as 101%. Accounting for publication bias substantially reduces the previously predicted effect of a decrease of 2 to 4 mm Hg in SBP/kg increase in BW, and consideration of the effects of current size may reduce these estimates further. In the present study, inverse, but not statistically significant, associations of BP with BW and birth length were seen only after adjustment for current size. In these models, there was a predicted decrease in SBP of 1.1 mm Hg/kg increase in BW, similar to estimates from studies comprising 1000 to 3000 participants and smaller than previous estimates.

Confounders including social class, maternal smoking, and maternal BP are likely to influence models relating BW and BP, but few studies have attempted to adjust for a range of potential confounders. In meta-analysis adjusted for publication bias, age, and sex, significant heterogeneity between studies remains and could be related to confounders and potential confounders.5 In meta-analysis adjusted for publication bias, age, and sex, significant heterogeneity between studies remains and could be related to confounders and potential confounders.

Table 3. Regression Models Adjusted for Sex With Systolic Blood Pressure in 8-Year-Olds as the Dependent Variable and Neonatal Measurements as Independent Variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted for Current Weight</th>
<th>Adjusted for Current Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CL</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>0.06</td>
<td>−0.19,0.32</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>0.29</td>
<td>−0.85,1.44</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>−0.07</td>
<td>−0.43,0.30</td>
</tr>
<tr>
<td>Ponderal index (kg/m³)</td>
<td>−0.010</td>
<td>−0.19,0.17</td>
</tr>
<tr>
<td>Chest circumference (cm)</td>
<td>0.10</td>
<td>−0.20,0.41</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>0.09</td>
<td>−0.15,0.33</td>
</tr>
<tr>
<td>Midarm circumference (cm)</td>
<td>0.30</td>
<td>−0.34,0.93</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>−0.14</td>
<td>−0.72,0.44</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>0.003</td>
<td>−0.001,0.007</td>
</tr>
<tr>
<td>Birthweight/placental weight</td>
<td>−0.57</td>
<td>−1.14,0.01</td>
</tr>
</tbody>
</table>

Models are shown unadjusted and with adjustment for current size. Adjustment for current weight was used for all variables except length and head circumference, which were adjusted for current height.

Figure 2. SBP in 8-year-olds according to quartiles of weight gain from birth to 8 years in the lowest and highest quartiles of BW.
differences in methodology. In the present study, error was minimized by prospective collection of information on demographic variables, including maternal education and family income, maternal characteristics such as ethnicity, weight, and height. BP at the time of the survey of 8-year-olds, parity, age, hemoglobin, diagnosis of diabetes, gestational diabetes, and hypertension during pregnancy. Exercise patterns, diet, and alcohol intake are not accounted for, and some residual confounding probably persists. However, these represent a wider range of variables than those included in other reported models. In our analyses, with adjustment for these variables, the estimated effect of BW or length at birth was slightly reduced and was not statistically significant, whereas the relationship with current weight, height, or BMI was independent of these possible confounders.

Associations between 8-year-olds’ BP or BW and other parental characteristics, including data from fathers, were examined but not included in multivariate models because missing values reduced the sample size. Mothers’ and fathers’ BWs were not available for all mother-child pairs in whom BP was measured at age 8 years. Neither of these variables was significantly related to BP in 8-year-olds but both variables significantly and independently predicted BW in children, as has been reported previously12 (mother’s BW, \( b = 0.20; 95\% \text{ CL: 0.04, 0.13}; P < 0.0001 \); father’s BW, \( b = 0.10; 95\% \text{ CL: 0.04, 0.13}; P < 0.001 \); adjusted \( R^2 = 0.085 \)). In the subset for whom data from fathers were available, SBP at age 8 years was predicted independently (adjusted \( R = 0.11 \)) by mothers’ (\( b = 0.11; 95\% \text{ CL: 0.04, 0.18}; P = 0.004 \)) and fathers’ (\( b = 0.08; 95\% \text{ CL: 0.02, 0.15}; P = 0.015 \)) SBP and children’s BMI (\( b = 0.97; 95\% \text{ CL: 0.58, 1.36}; P < 0.001 \)). The findings suggest that current body size, genetic determinants,13 and behavior patterns14 within families are more important predictors of BP at age 8 years than measures of size at birth.

Associations between lower BW and higher maternal BP in pregnancy15 or in middle-age16 have been recognized, but relationships between BW and later BP in offspring have also been reported to be independent of maternal BP.17 A family history of hypertension in men18 has been associated with smaller body size at birth. In the present study, we adjusted for maternal BW at the time of the survey of 8-year-olds and for the presence of hypertension in pregnancy and found no significant independent relationship between BP in 8-year-olds and size at birth.

Head circumference, length at birth, and ponderal index, as well as placental weight and the ratio of BW/placental weight, have been used in examining size at birth and BP, usually with adjustment for current size.4 Abdominal girth19 and chest circumference20 have been examined less frequently. Inverse associations between BP and these measurements of fetal and placental size have been reported, although inconsistently.4,12,20,21 We examined a range of variables that measured body size at birth and thinness as indicated by abdominal, chest, mid-arm circumference, and triceps skinfold, but none of these significantly predicted BP at age 8 years, with or without adjustment for current size. These findings do not support the suggestion that thinness, as an indicator of fetal undernutrition, is an important determinant of outcomes related to later cardiovascular risk as predicted by findings at age 8 years.22

We have previously reported associations between fetal growth and BP in 6-year-olds in the Raine cohort23 using conditional \( z \) scores of femur length and head and abdominal circumferences determined from multiple ultrasound examinations between 18 and 38 weeks of gestation. Fetal femur length, but not head or abdominal circumference, adjusted for current height or weight, was significantly related inversely to BP at age 6 years. A recent report of an association between shorter thigh length and increased risk for type 2 diabetes (http://www.americanheart.org/presenter.jhtml?ididentifi er=3009764) suggests that antenatal femur length warrants further study. Conditional \( z \) scores were available for only 360 8-year-olds and, although there was a negative relationship with SBP, this was not statistically significant in this subset, with or without adjustment for current size.

Analysis of data from 6-year-olds in the Raine cohort did not examine maternal factors other than smoking.24 BP was higher in children whose mothers smoked during pregnancy, and an inverse relation with BW was seen only in children whose mothers who had never smoked. In separate models in the current analysis, among the 599 8-year-old children whose mothers had never smoked, 478 whose mothers were ex-smokers, and the 340 whose mothers smoked during pregnancy, BW was not a significant predictor of SBP at age 8 years in any group, and there were no significant interactions with smoking status.

In our earlier analyses of data from the Raine cohort,25 models unadjusted for current weight showed no statistically significant association between BW and BP, in agreement with the present analysis. The relationship became statistically significant at age 3 and 6 years, but not at age 1 year, only after inclusion of current weight in the model, and it predicted a decrease of 2.3 mm Hg in SBP/kg of BW.25 It is important to note that the models used for the data from 8-year-olds included adjustment for sex, so regression coefficients will not be directly comparable. However, among 8-year-olds, adjustment for sex and current weight predicted a decrease of 1.1 mm Hg/kg of BW, showing a similar, but not statistically significant, effect to the earlier analyses. Analyses in 8-year-olds and in previous surveys25 agreed in showing no statistically significant interaction between BW and BP, and the sign of the regression coefficient was consistently negative in these models. The previous analyses showed that current weight was the best predictor of BP at ages 1, 3, and 6 years, consistent with the data from 8-year-olds. Thus, there is overall similarity between the analyses in 8-year-olds and the earlier models, with the main difference being failure to reach statistical significance in models adjusted for current weight, remembering, however, that these models at the age of 8 years were additionally adjusted for sex. In the present analyses, we have extended the models to include adjustment for a range of confounders and have shown no statistically significant associations between BW and BP in 8-year-olds.

Although we did not find statistically significant relationships between size at birth and BP in 8-year-olds, amplification with age has been suggested.26 Without adjustment for
publication bias, Schluchter\(^{6}\) reported that an increase of 1 kg in BW predicts lower SBP by \(-0.3\) mm Hg for every 10 years of increase in age. However, the relationship was no longer statistically significant after adjustment for publication bias, whereas the effect of publication bias was independent of age. Follow-up of the Raine cohort may reveal stronger relationships between antenatal growth or size at birth and BP, possibly mediated by adverse lifestyle choices related to diet, physical inactivity, and weight gain.\(^{27}\)

Our findings suggest that postnatal change in size is the major determinant of BP in these 8-year-olds and that this association is unrelated to BW. Overweight and obesity in childhood and adolescence lead to an increase in risk factors for cardiovascular disease, including BP.\(^{28}\) However, the relationship between BP and measures of adiposity is a continuum, so that risk of higher BP applies even in children not classified as overweight or obese.\(^{29}\) Given the worldwide increase in rates of overweight and obese children, and the tracking of obesity and BP to adult life, these results emphasize the need to prevent excess weight gain in early childhood.

**Perspectives**

Commonly, BW is a predictor of later BP only in models that include adjustment for current weight and few models have included adjustment for a range of prospectively collected possible confounding variables. In a cohort of 8-year-olds, we found no statistically significant association between BW and BP with or without adjustment for current weight or with adjustment for a range of possible confounders. The dominant variable in the regression models was current weight, suggesting that postnatal change in weight is the principal determinant of BP in these children. Our findings reinforce the importance of weight control in childhood with the potential for long-term benefits, because of the well-recognized tracking of BP and overweight or obesity to adult life.

**Acknowledgments**

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**References**

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