The relationship between birth weight and pulse pressure in children: cross-sectional study

Running title: Birth weight & pulse pressure

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Summary

This cross-sectional study investigates the relationship between birth weight and pulse pressure in childhood, after adjusting for mean blood pressure values and for potential confounding factors. Blood pressure was measured in 937 schoolchildren, free from cardiovascular disease, aged between 6 and 16. Pulse pressure was estimated as the difference between the 24-hour mean systolic and diastolic blood pressure values. Linear regression showed a significant negative association between birth weight and log-transformed pulse pressure, which after gender specific analyses was found to be restricted to the girls in the study (adjusted regression coefficient log mmHG per Kg -0.06, 95% CI -0.09 to -0.03). A previous investigation of this cohort reported a significant negative association between birth weight and both systolic and diastolic blood pressure, again restricted to the girls in the cohort. The results of the present study provide limited support for the hypothesis that pulse pressure in childhood is determined in utero, particularly for females. However, as little research has been published in this area, further investigation is required and in particular it would be important to assess whether such gender differences are apparent in other cohorts.

Keywords: Blood pressure, pulse pressure, birth weight, Barker hypothesis
Introduction

While elevated systolic and/or diastolic blood pressure is recognised as a major risk factor for cardiovascular complications,[1] more recent research has suggested that increased pulse pressure, defined as the difference between systolic and diastolic blood pressure, may also be an important component of increased risk of cardiovascular disease, particularly when in conjunction with raised systolic blood pressure. [2-3] It is generally accepted that the importance of pulse pressure in adulthood is in relation to the well demonstrated association between increased pulse pressure and increased arterial stiffness. Pulse pressure normally changes little in childhood as both systolic and diastolic pressure increase with height, but there has been little research into arterial stiffness in subgroups of children at risk of blood pressure problems.

It has been proposed that the risk of adverse health in middle age, including hypertension, cardiovascular disease and diabetes, is ‘programmed’ by impaired fetal development.[4] In particular, a number of epidemiological studies have demonstrated a negative correlation between birth weight and blood pressure in adulthood,[5-7] although the association remains controversial.[8-9] Evidence also exists for such a relationship in childhood,[10-12] although has been suggested to vary with age and gender.[13]

Much less is known regarding the relationship between fetal growth and pulse pressure, particularly in childhood. A recent study by Lurbe et al.[14] however, suggested an association between birth weight and ambulatory pulse pressure in a group of 300 healthy adolescents. Cheung et al. found some evidence of increased arterial stiffness, measured by pulse wave velocity, rather than using pulse pressure as a surrogate, in babies born small for gestational age. [15] Although not measured in that study, it would suggest that there may be subtle differences in pulse pressure in children of different birth weights. This present study was designed to investigate further the hypothesis that pulse pressure in childhood may be predicted by birth weight, after adjusting for potential confounding factors such as age, current blood pressure, gestation and gender. Previous studies using the same data have shown a negative association between birth weight and mean 24-hour systolic blood pressure, although the
significant association was shown in girls, but not boys and in children aged 11 years or older, but not in the younger age group [13].
Materials and Methods

Twenty six of the 28 schools approached in Newcastle upon Tyne agreed to participate in this study [13, 16-17]. Certain age groups were targeted within each school and a doctor (JJOS) visited the chosen class to explain the study to the children. The participation rate of the target years varied from 7-75%. Parents were requested to complete a questionnaire for information on birth weight and gestation of the child. The reported data on birth weight were confirmed for over 600 cases by retrieving the original hospital birth records.[18] Recalled and recorded birth weights were highly correlated (r=0.95). Children reported on the questionnaire to have a history of renal or cardiac problems were not enrolled into the study. A total of 1129 children were recruited, although eight children were excluded due to either fainting during the validation procedure and not wearing the monitor (n=5) or because they did not produce sufficient valid systolic readings (n=3).

The study used a TM-2421 device (A & D Japan) giving Korotkoff readings to measure 24-hour blood pressure. This method should in theory replicate the clinical measurement of blood pressure. However, it is very difficult to validate ambulatory readings of systolic and diastolic pressures and the recommendations of the British Hypertension Society are that devices should be validated at rest, as was done for the device used in this study. Due to the potential problems of measuring systolic and diastolic blood pressure when active, children were asked to remain still while the reading was taken. Oscillometric readings were also available, but were excluded due to the poor British Hypertension Society grades obtained. Measurements were taken every thirty minutes during the day and every sixty minutes between 22:00 and 07:00. The protocol has been described in detail elsewhere. [13] All readings were accepted unless the recorded systolic blood pressure was ≤50 or ≥200 mm HG; the diastolic blood pressure was ≤30 or ≥100 mm HG and the heart rate ≥200 or ≤ 30 beats per minute. If more than 25% of the recordings for an individual were erroneous all data from that individual were excluded. Pulse pressure was estimated as the difference between the mean 24-hour systolic and diastolic blood pressure measurements, but was log-transformed to normality.
Linear regression was used to model the relationship between log-transformed pulse pressure and other variables, with interactions tested using a likelihood ratio test. Current age was modelled using fractional polynomials,[19] to account for non-linearity in the relationship with pulse pressure. Linearity in the relationship between birth weight and pulse pressure was also checked using this method. The coefficients from the Lucas regression model for the change from standardised birth weight to current weight,[20] after adjusting for height and body mass index were calculated to estimate the association between childhood weight gain and pulse pressure.

Additional linear regression assumptions and goodness of fit were checked. Analyses were performed using the statistical software package Stata, version 8.0 (StataCorp: College Station, TX).

Ethical approval for this study was given by the Joint Research Ethics Committee of Newcastle and North Tyneside Local Health Authority. Signed consent was obtained from the parent or guardian of each child.
Results

After applying the exclusion criteria (resulting in 145 exclusions) and eliminating a further 39 children for whom either mean systolic or mean diastolic blood pressure was unavailable, 937 children (528 girls) were included in the analysis. Table 1 details the blood and pulse pressure values and other descriptive data by gender. Log-transformed pulse pressure was significantly higher in boys than in girls and in those children aged over 10 years of age then the younger group (p<0.0001). Both mean systolic and mean diastolic blood pressure were significantly correlated with log-transformed mean pulse pressure (r= 0.86 and r= -0.16 respectively).

There was a significant negative unadjusted association between birth weight and log-transformed pulse pressure (Table 2). However, this was restricted to the girls in the study (r=-0.06 log mmHG per Kg, 95% CI -0.08 to -0.03, p<0.001), with no association being seen among the boys. The negative association in girls remained after adjustment for both systolic (r=-0.02 log mmHG per Kg, 95% CI -0.03 to -0.01, p=0.004) and diastolic (r=-0.06 log mmHG per Kg, 95% CI -0.08 to -0.03, p<0.001) mean blood pressure. Similar results were seen after adjustment for current age, height and weight and gestational age. No evidence of non-linearity in the relationship between birth weight and pulse pressure was found.

Of the other explanatory variables in the adjusted analysis, only current weight was a significant predictor of log-transformed pulse pressure in girls (r=0.004 log mmHG per Kg, 95% CI 0.02 to 0.006, p=0.001), while only current height was a significant predictor in boys (r=0.01 log mmHG per cm, 95% CI 0.003 to 0.10, p<0.001). Current weight has previously been shown to be significantly associated with systolic blood pressure in both boys and girls in this study group [13], but was not significantly associated with diastolic blood pressure in either boys (p=0.14) or girls (p=0.06). Similar results were seen for body mass index and pulse pressure, although body mass index was a significant predictor of both systolic and diastolic blood pressure in boys (p=0.04 and p<0.001 respectively), but not in girls (p=0.81 and 0.76 respectively).
The regression models showed little evidence of an association between childhood weight gain (adjusted for current height and body mass index) and pulse pressure in either girls (p=0.07) or boys (p=0.31).
Discussion

Although blood pressure has long been recognised as a risk factor for cardiovascular events,[1] the relative effect of pulse pressure has only more recently been investigated. The evidence so far suggests that, while having a lesser effect than systolic blood pressure,[21] pulse pressure, in middle and old age, may be an independent predictor in determining cardiovascular risk,[2-3] possibly by altering haemostasis or endothelial function.[22]

While remaining controversial, a weight of evidence exists to suggest a negative association between birth weight and blood pressure in later life.[5-7] Similarly, evidence exists for such a relationship in children,[10-12] although a previous study of this cohort suggested that the relationship may vary with age and gender.[13]

Much less is known regarding the possibility that pulse pressure may be in part determined by fetal growth. A recent study of adult type 1 diabetes patients found an inverse relationship between birth weight and pulse pressure,[23] although this observation cannot be generalised to the wider population. In utero nutrient restricted young adult sheep have also been shown to have increased pulse pressure, although their birth weights were unaffected.[24]

In what appears to be the only previous study of birth weight and pulse pressure in childhood, Lurbe et al. observed that birth weight was inversely related to ambulatory pulse pressure in a study of a 300 healthy children aged between 10 and 18 years.[14] While our results are consistent with those of Lurbe et al. further analysis demonstrated that the relationship was restricted to the girls in our cohort. In a previous investigation of this cohort,[13] we observed a significant inverse correlation between birth weight and childhood systolic and diastolic blood pressure, a relationship which was again restricted to the girls in the study. In the current study, the relationship between birth weight and pulse pressure remained after adjustment for both systolic and diastolic mean blood pressure, although as pulse pressure is estimated as the difference between systolic and diastolic blood pressure, it will be ‘mathematically coupled’ to both blood pressure variables.[25] Such adjustments may in turn lead to misleading inferences regarding the adjusted associations between outcomes and explanatory
variables. This is particularly likely to be have the reason for the reduced coefficient for the relationship between birth weight and pulse pressure after adjustment for systolic blood pressure, which was highly correlated with pulse pressure. This also raises the possibilities that pulse pressure may be acting as a surrogate for systolic blood pressure, or that systolic blood pressure lies on the causal pathway between fetal growth and pulse pressure. Although not linked to ‘mathematical coupling’, a similar problem may occur with the adjustments for height and weight, which are also possibly on the same causal pathway and may not be true confounding factors.

While the results of this investigation should not be interpreted as a causal association, if the association between birth weight and pulse pressure is a true relationship, further research is required into the mechanism or mechanisms responsible.

The reasons for the gender differences in our study are not known and were not formally addressed. It is possible that pubertal development may play a role, although, as with our previous study, this would not explain the gender differences in the relationship between birth weight and blood pressure reported in 5-7 year olds. Whilst the possibility that the gender difference is a chance finding cannot be ruled out, the implication of such an observation is that gender differences in risk factors for disease should be investigated and, if true gender differences are involved, that they may be used to inform studies of the mechanisms of such differential effects.

Blood pressure, and hence pulse pressure, measurement is prone to errors, particularly in children, but is unlikely to have introduced a systematic bias to this investigation.

In summary, the data presented here suggest that a significant relationship between birth weight and pulse pressure in childhood may be restricted to females. However, as little research has been published in this area, further investigation is required.
Acknowledgements

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References


26 Tu YK, Gilthorpe MS, Griffiths GS. Is reduction of pocket probing depth correlated with the baseline value or is it ‘mathematical coupling’? *J Dent Res* 2002;81:722-6.


Table 1. Descriptive statistics, by gender, for the study population

<table>
<thead>
<tr>
<th></th>
<th>Boys (n=409)</th>
<th>Girls (n=528)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Range</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.5 (9.0-13.6)</td>
<td>7.0 to 16.0</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.4 (3.1-3.8)</td>
<td>1.4 to 5.0</td>
</tr>
<tr>
<td>Current height (cm)</td>
<td>145.6 (134.3-158.5)</td>
<td>110.3 to 187.0</td>
</tr>
<tr>
<td>Current weight (kg)</td>
<td>38.0 (30.0-50.0)</td>
<td>19 to 100</td>
</tr>
<tr>
<td>Body mass index</td>
<td>17.7 (16.3-19.8)</td>
<td>12.3 to 30.3</td>
</tr>
<tr>
<td>24-h SBP, mm/HG</td>
<td>111.8 (104.9-117.6)</td>
<td>88.7 to 147.2</td>
</tr>
<tr>
<td>24-h DBP, mm/HG</td>
<td>61.7 (58.4-64.8)</td>
<td>48.7 to 77.3</td>
</tr>
<tr>
<td>24-h Pulse pressure</td>
<td>50.0 (44.0-56.2)</td>
<td>30.1 to 82.3</td>
</tr>
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</table>

IQR, Interquartile Range
Table 2. Relationship between birth weight and pulse pressure

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient&lt;sup&gt;1&lt;/sup&gt;</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>-0.03</td>
<td>-0.05 to -0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Girls only</td>
<td>-0.06</td>
<td>-0.08 to -0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Boys only</td>
<td>-0.02</td>
<td>-0.05 to 0.02</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Adjusted&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>-0.02</td>
<td>-0.04 to 0.003</td>
<td>0.09</td>
</tr>
<tr>
<td>Girls only</td>
<td>-0.05</td>
<td>-0.08 to 0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Boys only</td>
<td>0.0001</td>
<td>-0.04 to 0.04</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Adjusted&lt;sup&gt;3&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>-0.04</td>
<td>-0.06 to -0.01</td>
<td>0.003</td>
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<td>Girls only</td>
<td>-0.06</td>
<td>-0.09 to -0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Boys only</td>
<td>-0.02</td>
<td>-0.06 to 0.01</td>
<td>0.18</td>
</tr>
</tbody>
</table>

<sup>1</sup> Regression coefficient per log(pulse pressure). Birth weight measured in kg.

<sup>2</sup> Adjusted for current age and gestational age.

<sup>3</sup> Adjusted for current age, body mass index, current height, and gestational age.
### Table 3

#### What is known on this topic

Evidence exists for an inverse relationship between birth weight and blood pressure, both in adults [5-7] and in children [9-11]. Less is known regarding the potential link between birth weight and pulse pressure, although a recent study reported a negative association [13].

#### What this study adds

We found a significant negative association between birth weight and pulse pressure, although this association was restricted to the girls in the study.

Our results add to the evidence that birth weight may affect pulse pressure. However, there may be gender specific effects on such relationships that require further research.