Developmental origins of cardiovascular risk in Jamaican children: The Vulnerable Windows Cohort Study

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Both intra-uterine and early childhood development contribute to the risk of developing CVD in adult life. We therefore evaluated the maternal, placental, fetal, birth, infant and childhood determinants of cardiovascular risk in a cohort of Afro-Jamaican children. The Vulnerable Windows Cohort is a longitudinal survey of 569 mothers and their offspring recruited from the first trimester. The offspring’s anthropometry was measured at birth, at 6 weeks, every 3 months to 1 year and then every 6 months. At mean age 11.5 years, fasting blood was sampled for glucose, insulin and lipids. Analyses were confined to 296 women and their offspring who had complete data. Waist circumference (WC) was related to maternal weight and BMI, placental weight and to the size of the offspring in utero, at birth and the rate of growth in childhood ($P<0.05$). Total cholesterol, TAG and glucose concentrations were unrelated to maternal, placental, fetal, neonatal and childhood measurements. Fasting insulin and homeostasis model assessment of insulin resistance were related to maternal weight and BMI ($P<0.05$), but not after adjusting for WC. HDL-cholesterol was inversely related to placental and birth weight, and inversely related to weight and BMI throughout childhood ($P<0.001$), but not after adjusting for WC. Systolic blood pressure was directly related to maternal weight, child’s height, weight and BMI ($P<0.005$), but not after adjusting for WC. Systolic blood pressure and fasting glucose concentration were inversely related to birth weight in boys but directly associated in girls. We concluded that maternal anthropometry during pregnancy, fetal size, and childhood growth rate contribute to cardiovascular risk factors in childhood.

**Growth: Fetus: Body composition: Cardiovascular risk factors**

Maternal anthropometry is positively related to fetal growth and weight at birth. Birth weight itself is associated with the risk of developing diabetes and CVD in adulthood¹¹. Birth weight and anthropometry are markers for altered organ structure and function, and these structural and functional set points and capacities may underlie the increased susceptibility to disease³⁴. Reduced infant growth and rapid weight gain through childhood are further independent risk factors for diabetes and CVD⁵⁶.

CVD patterns and rates vary widely among ethnic groups, in part due to exposure to classical risk factors, but also to susceptibility to these risk factors⁷⁹. An example is the difference in the BMI associated with minimum risk of diabetes and CVD in different populations⁹¹⁰. Very little information on markers and mechanisms of underlying susceptibility is available for African-origin populations. The ‘Vulnerable Windows Cohort Study’ was established in the Tropical Metabolism Research Unit, University of the West Indies in 1993 as an observational study to describe such susceptibility to cardiovascular risk in black Jamaicans¹¹.

We hypothesised that small maternal size, small birth size and increased growth rates during early childhood are associated with increased cardiovascular risk in later childhood. Thus, in this cohort of Jamaican children aged 12 years, we describe the maternal, placental, fetal, birth, infant and childhood determinants of cardiovascular risk, specifically waist circumference, blood glucose, serum insulin, serum lipids and blood pressure.

**Experimental methods**

**Study design and subjects**

As previously described¹¹, in 1992–3, 712 women attending the antenatal clinic at the University Hospital of the West Indies, Kingston, Jamaica, were invited to participate in the Vulnerable Windows Cohort Study. Women who were aged between 15 and 40 years, were 7–10 weeks pregnant, sure of their last menstrual period (which was confirmed by a 14-week ultrasound), and without systemic illnesses (for example, pre-eclampsia and diabetes), or genetic abnormality (for example, sickle cell disease) were included. After eighty-two pregnancy losses, fifty-six withdrawals for reasons such as work constraints and migration, and five sets of twins were
excluded, 569 babies were included in the study. All women were offered transport to and from the hospital to enhance participation. For the present report, data analysis was confined to 296 women and their offspring who were seen within 2 years of every scheduled visit between birth and age 12 years. Each mother gave written informed consent. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee of the University of the West Indies.

**Measurements**

Weight was measured to the nearest 0·01 kg using a Weylux beam balance (CMS Weighing Equipment Ltd, London, UK). Height was measured to the nearest 0·1 cm with a stadiometer (CMS Weighing Equipment Ltd)\(^{(11)}\). Abdominal ultrasound was performed at 14, 17, 20, 25, 30 and 35 weeks of gestation using a linear probe (ATL UltraMark IV; Philips Medical Systems North America, Bothell, WA, USA). Fetal measurements including abdominal circumference were estimated sonographically at all visits. The average of three measurements was used. Placental volume was measured sonographically at 14, 17 and 20 weeks\(^{(12)}\).

Anthropometric measurements of the infant were obtained within 24 h of delivery. We measured birth weight with a Health-o-Meter \(^{®}\) 459 scale (Pelstar LLC, Bridgeview, IL, USA), placental weight with an electronic balance (Digimail 800100; Soehnle, Murrhardt, Germany), crown–heel length with a length board (Holtain Ltd, Crymych, Dyfed, UK) and head circumference with a fibreglass tape. We measured offspring anthropometry at birth, at 6 weeks, every 3 months to 2 years and then every 6 months. BMI was calculated by dividing body mass (kg) by the square of height (m\(^2\)). Blood pressure was measured every 6 months from the age of 1 year using an oscillometric sphygmomanometer\(^{(11)}\). Inter- and intra-observer variability was measured every 3 months, followed by training and recertification for any observer whose scores were not acceptable. Staging of the pubic hair and breast development was done according to the method of Marshall & Tanner\(^{(13,14)}\). Testicular volume was determined using the manufacturer’s equations and fat mass by difference from body weight.

**Assays**

Plasma glucose was measured by the glucose oxidase system. Total cholesterol, HDL-cholesterol and TAG were measured by enzymic techniques using a VP biochromatic analyser (Abbott, Irving, TX, USA). Plasma insulin was measured with an immunometric assay (Immulite Insulin; Diagnostic Products Corporation, Los Angeles, CA, USA). The assay had an analytical sensitivity of 2 μIU/ml and the intra-assay CV was < 8.0%. The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated as the product of insulin and glucose divided by 22·6\(^{(15)}\).

**Statistical analysis**

Insulin, HOMA-IR and TAG had skewed distributions and were log transformed towards normality for analysis. Growth was measured in three time intervals: birth to 6 months; 6 months to 2 years; and 2 years to age 11 years.

**Table 1. Maternal, placental, fetal, neonatal, infant and childhood measurements**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Birth weight (g)</th>
<th>Maternal measurements at first antenatal visit</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Pregnancy weight gain (kg per 4 weeks)</th>
<th>Maternal, placental, fetal, neonatal, infant and childhood measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Boys (n 134)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Girls (n 162)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Outcome variables**

- Fasting insulin (pmol/l)\(^*\): 29·4 1·9 43·2 2·1
- Fasting glucose (mmol/l): 4·9 0·4 4·8 0·4
- HOMA-IR\(^*\): 6·3 2·0 9·1 2·1
- Total cholesterol (mmol/l): 4·4 0·8 4·4 0·8
- HDL-cholesterol (mmol/l): 1·3 0·3 1·3 0·3
- TAG (mmol/l)\(^*\): 0·5 1·6 0·6 1·7
- Systolic blood pressure (mmHg): 101·6 6·1 99·6 5·5

**Statistical analysis**

Insulin, HOMA-IR and TAG had skewed distributions and were log transformed towards normality for analysis. Growth was measured in three time intervals: birth to 6 months; 6 months to 2 years; and 2 years to age 11 years.
It was defined as the amount by which the size at the end of a
time interval exceeded that which would have been predicted
by linear regression using the measurements available at the
beginning of the interval\(^{(10)}\). This approach ensures that the
growth indices are uncorrelated. Multiple regression analyses
including age and sex were used to measure the associations
of cardiovascular risk factors with maternal factors, placental,
fetal and neonatal size, and infant and childhood growth. We
used outcomes and predictors in standardised form (i.e. for a
standardised score, a value of 0 corresponds to the mean and a
value of 1 corresponds to 1 SD above the mean and so on). To test for similarity of effects between boys and girls
we used product terms of sex with anthropometric variables.
We always adjusted risk factors for age at the clinic visit.

\(*P<0.05\) was considered statistically significant. SPSS 15.0
for Windows (SPSS, Inc., Chicago, IL, USA) was used for
the statistical analyses.

### Results

The 296 subjects studied were similar to the other members of
the cohort in maternal age, height, weight, BMI and socio-
-economic status. They were not different in birth length,
head circumference or placental weight, but were 129 g hea-
tier in weight \((P=0.004)\) and 3.2 d older in gestational age
at birth \((P=0.006)\).

Mean values for maternal, placental, fetal, newborn and
postnatal measurements and anthropometric and biochemical
measurements are shown in Table 1. As expected, males
tended to be larger until age 11 years, at which stage more
girls had started their pubertal growth spurt and had a
higher BMI, fat mass and percentage body fat. Including
measurements made subsequent to venepuncture, the median
age at reaching Tanner stage 3 for pubic hair development
was 11.1 years in girls and 12.8 years in boys.

Tables 2 and 3 show the associations of the eight outcomes
measured with maternal, placental, fetal and newborn size.
Table 4 extends this to include infant and childhood growth.
We describe the outcomes in sequence.

#### Waist circumference

Waist circumference in the children was positively correlated
with maternal size in the first trimester, placental weight, size
of the fetus in the third trimester and with the length and
weight of the infant at birth (Table 2). Faster rate of growth
of children also predicted waist circumference (Table 4;
Fig. 1(a)). Thus, waist size in children was positively related
to maternal size, placental size, fetal size and birth size,
as well as growth rate in infancy and childhood.

Fasting plasma insulin and homeostasis model assessment of
insulin resistance

Fasting insulin was directly related to maternal weight and
BMI in the first trimester (Table 2). However, these associ-
ations were no longer statistically significant following adjust-
ment for waist circumference measured at clinic (Table 3).
Fasting insulin was positively related to rate of postnatal
growth in height, weight and BMI (Table 4). Thus, fasting
insulin was directly related to maternal size in early pregnancy
and growth in childhood.

HOMA-IR followed closely the associations seen with fast-
ing insulin (Tables 2 and 4). The association of HOMA-IR
with height, weight and BMI through childhood is illustrated
in Fig. 1(b).

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**Table 2. Regression coefficients between maternal, placental, fetal and neonatal measurements of 296 Afro-Jamaican children and their measurements made at clinic\(†\)**

<table>
<thead>
<tr>
<th></th>
<th>Waist circumference</th>
<th>Fasting insulin</th>
<th>Fasting glucose</th>
<th>HOMA-IR</th>
<th>Total cholesterol</th>
<th>HDL-cholesterol</th>
<th>TAG</th>
<th>Systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at booking (years)</td>
<td>0.054</td>
<td>0.028</td>
<td>0.009</td>
<td>0.006</td>
<td>-0.018</td>
<td>-0.024</td>
<td>-0.019</td>
<td>0.041</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.144*</td>
<td>0.008</td>
<td>-0.053</td>
<td>-0.010</td>
<td>0.043</td>
<td>-0.104</td>
<td>0.056</td>
<td>0.063</td>
</tr>
<tr>
<td>Weight at booking (kg)</td>
<td>0.239*</td>
<td>0.134*</td>
<td>-0.036</td>
<td>0.106</td>
<td>-0.016</td>
<td>-0.071</td>
<td>0.031</td>
<td>0.119*</td>
</tr>
<tr>
<td>BMI at booking (kg/m²)</td>
<td>0.203*</td>
<td>0.128*</td>
<td>-0.022</td>
<td>0.106</td>
<td>-0.030</td>
<td>-0.043</td>
<td>0.015</td>
<td>0.104</td>
</tr>
<tr>
<td>Pregnancy weight gain (kg per 4 weeks)</td>
<td>0.065</td>
<td>-0.082</td>
<td>-0.011</td>
<td>-0.076</td>
<td>0.042</td>
<td>0.041</td>
<td>-0.006</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Placental measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-week volume (ml)</td>
<td>0.010</td>
<td>-0.096</td>
<td>-0.042</td>
<td>-0.094</td>
<td>-0.107</td>
<td>0.021</td>
<td>-0.119</td>
<td>-0.039</td>
</tr>
<tr>
<td>17-week volume (ml)</td>
<td>-0.087</td>
<td>-0.116</td>
<td>-0.048</td>
<td>-0.126*</td>
<td>0.004</td>
<td>0.005</td>
<td>-0.097</td>
<td>-0.090</td>
</tr>
<tr>
<td>20-week volume (ml)</td>
<td>0.060</td>
<td>0.001</td>
<td>-0.039</td>
<td>-0.014</td>
<td>0.001</td>
<td>0.054</td>
<td>-0.036</td>
<td>-0.005</td>
</tr>
<tr>
<td>Weight at delivery (g)</td>
<td>0.140*</td>
<td>0.076</td>
<td>0.008</td>
<td>0.062</td>
<td>-0.068</td>
<td>-0.129*</td>
<td>-0.006</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>Fetal abdominal circumference (mm)</strong></td>
<td>0.064</td>
<td>-0.021</td>
<td>0.051</td>
<td>0.008</td>
<td>0.026</td>
<td>-0.065</td>
<td>0.064</td>
<td>0.072</td>
</tr>
<tr>
<td>14 weeks</td>
<td>0.036</td>
<td>-0.031</td>
<td>0.077</td>
<td>-0.012</td>
<td>0.000</td>
<td>-0.078</td>
<td>0.063</td>
<td>0.018</td>
</tr>
<tr>
<td>25 weeks</td>
<td>0.144*</td>
<td>-0.022</td>
<td>-0.010</td>
<td>-0.031</td>
<td>0.019</td>
<td>-0.113</td>
<td>0.002</td>
<td>0.067</td>
</tr>
<tr>
<td><strong>Newborn measurements</strong></td>
<td>0.189*</td>
<td>0.008</td>
<td>0.036</td>
<td>0.011</td>
<td>0.057</td>
<td>-0.127*</td>
<td>0.033</td>
<td>0.022</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.093</td>
<td>0.015</td>
<td>0.012</td>
<td>0.020</td>
<td>0.092</td>
<td>-0.049</td>
<td>-0.002</td>
<td>-0.040</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>0.130*</td>
<td>0.029</td>
<td>0.042</td>
<td>0.025</td>
<td>0.040</td>
<td>-0.075</td>
<td>0.012</td>
<td>-0.044</td>
</tr>
<tr>
<td>Gestation at delivery (d)</td>
<td>0.091</td>
<td>0.078</td>
<td>0.068</td>
<td>0.085</td>
<td>0.090</td>
<td>0.010</td>
<td>-0.052</td>
<td>-0.054</td>
</tr>
</tbody>
</table>

HOMA-IR, homeostasis model assessment of insulin resistance.

\* \(P<0.05\).

\(†\) Analyses are adjusted for sex and age at clinic visit. All measurements are in standardised form, i.e. for a standardised score, a value of 0 corresponds to the mean and a
value of 1 corresponds to 1 SD above the mean and so on.
Maternal measurements

Table 3. Regression coefficients of maternal, placental, fetal and neonatal measurements of 296 Afro-Jamaican children and their measurements made at clinic

<table>
<thead>
<tr>
<th>Maternal measurements</th>
<th>Fasting insulin</th>
<th>Fasting glucose</th>
<th>HOMA-IR</th>
<th>Total cholesterol</th>
<th>HDL-cholesterol</th>
<th>TAG</th>
<th>Systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at booking (years)</td>
<td>0·000</td>
<td>-0·004</td>
<td>-0·004</td>
<td>-0·019</td>
<td>-0·006</td>
<td>-0·029</td>
<td>0·014</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0·048</td>
<td>-0·040</td>
<td>0·036</td>
<td>0·019</td>
<td>-0·069</td>
<td>0·017</td>
<td>0·041</td>
</tr>
<tr>
<td>Weight at booking (kg)</td>
<td>0·097</td>
<td>-0·048</td>
<td>0·088</td>
<td>-0·030</td>
<td>0·006</td>
<td>-0·017</td>
<td>0·021</td>
</tr>
<tr>
<td>BMI at booking (kg/m²)</td>
<td>0·075</td>
<td>-0·039</td>
<td>0·069</td>
<td>-0·037</td>
<td>0·026</td>
<td>0·022</td>
<td>0·008</td>
</tr>
<tr>
<td>Pregnancy weight gain (kg per 4 weeks)</td>
<td>-0·106</td>
<td>-0·008</td>
<td>-0·105</td>
<td>0·034</td>
<td>0·064</td>
<td>-0·023</td>
<td>0·001</td>
</tr>
</tbody>
</table>

Placental measurements

Table 4. Regression coefficients of size at birth and childhood growth of 296 Afro-Jamaican children and their measurements made at clinic

<table>
<thead>
<tr>
<th>Placental measurements</th>
<th>Fasting insulin</th>
<th>Fasting glucose</th>
<th>HOMA-IR</th>
<th>Total cholesterol</th>
<th>HDL-cholesterol</th>
<th>TAG</th>
<th>Systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-week volume (ml)</td>
<td>-0·049</td>
<td>-0·049</td>
<td>-0·050</td>
<td>-0·103</td>
<td>0·027</td>
<td>-0·121</td>
<td>-0·058</td>
</tr>
<tr>
<td>17-week volume (ml)</td>
<td>0·051</td>
<td>-0·045</td>
<td>0·061</td>
<td>0·009</td>
<td>-0·024</td>
<td>-0·082</td>
<td>-0·061</td>
</tr>
<tr>
<td>20-week volume (ml)</td>
<td>0·025</td>
<td>-0·040</td>
<td>0·031</td>
<td>-0·004</td>
<td>-0·037</td>
<td>0·051</td>
<td>-0·030</td>
</tr>
<tr>
<td>Weight at delivery (g)</td>
<td>0·038</td>
<td>0·007</td>
<td>0·040</td>
<td>-0·081</td>
<td>-0·091</td>
<td>0·038</td>
<td>0·007</td>
</tr>
</tbody>
</table>

Fetal abdominal circumference (mm)

| 14 weeks               | -0·022          | 0·043          | 0·011   | 0·028            | -0·045          | 0·057| 0·038                  |
| 25 weeks               | -0·019          | 0·071          | 0·016   | 0·002            | -0·069          | 0·061| -0·005                 |
| 35 weeks               | -0·013          | -0·016         | 0·011   | 0·010            | -0·072          | -0·028| 0·009                 |

Neonatal measurements

| Weight (kg)            | 0·030           | 0·038          | 0·040   | 0·040            | -0·075          | 0·010| -0·046                 |
| Length (cm)            | 0·064           | 0·028          | 0·079   | 0·074            | 0·027           | 0·032| -0·054                 |
| Head circumference (cm)| 0·069           | 0·050          | 0·073   | 0·023            | -0·040          | 0·022| -0·085                 |
| Gestation at delivery (d) | 0·100           | 0·074          | 0·111   | 0·078            | 0·039           | -0·077| -0·085                 |

Fasting plasma glucose

The highest observed fasting glucose concentration was 6·0 mmol/l, which occurred in one subject only. Fasting glucose was unrelated to maternal, placental, fetal and childhood measurements (Table 2). Growth in children was not associated with any influence on fasting glucose (Table 4).

Serum lipids

Total cholesterol concentration was unrelated to maternal, placental, fetal, newborn and childhood measurements (Table 2), or rate of growth during infancy and childhood (Table 4).

HDL-cholesterol concentration was inversely related to placental and birth weight (Table 2), but these associations were no longer statistically significant following adjustment for waist circumference measured at clinic (Table 3). It was also inversely related to weight and BMI in childhood (Table 4). The relationships of HDL-cholesterol and childhood height, weight and BMI are illustrated in Fig. 1(c).

Serum TAG concentrations were not predicted by any maternal, placental, fetal, newborn or childhood variables (Tables 2 and 4).

Table 4. Regression coefficients of size at birth and childhood growth of 296 Afro-Jamaican children and their measurements made at clinic

<table>
<thead>
<tr>
<th>Measurement of size and growth</th>
<th>Waist circumference</th>
<th>Fasting insulin</th>
<th>Fasting glucose</th>
<th>HOMA-IR</th>
<th>Total cholesterol</th>
<th>HDL-cholesterol</th>
<th>TAG</th>
<th>Systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>0·092</td>
<td>0·009</td>
<td>0·007</td>
<td>0·014</td>
<td>0·093</td>
<td>-0·049</td>
<td>0·000</td>
<td>-0·041</td>
</tr>
<tr>
<td>Growth: from 0 to 6 months</td>
<td>0·224***</td>
<td>0·062</td>
<td>0·014</td>
<td>0·064</td>
<td>0·051</td>
<td>-0·020</td>
<td>0·092</td>
<td>0·201***</td>
</tr>
<tr>
<td>Growth: from 6 months to 2 years</td>
<td>0·169</td>
<td>0·093</td>
<td>0·095</td>
<td>0·095</td>
<td>-0·105</td>
<td>0·034</td>
<td>0·010</td>
<td>0·209***</td>
</tr>
<tr>
<td>Growth: from 2 years to 11 years</td>
<td>0·241***</td>
<td>0·271***</td>
<td>0·082</td>
<td>0·286***</td>
<td>-0·156</td>
<td>-0·132</td>
<td>-0·029</td>
<td>0·161</td>
</tr>
<tr>
<td>Weight</td>
<td>0·187***</td>
<td>0·005</td>
<td>0·033</td>
<td>0·008</td>
<td>0·056</td>
<td>-0·126</td>
<td>0·032</td>
<td>0·022</td>
</tr>
<tr>
<td>Growth: from 0 to 6 months</td>
<td>0·215***</td>
<td>0·064</td>
<td>0·000</td>
<td>0·056</td>
<td>0·008</td>
<td>-0·015</td>
<td>0·114</td>
<td>0·195***</td>
</tr>
<tr>
<td>Growth: from 6 months to 2 years</td>
<td>0·363***</td>
<td>0·202***</td>
<td>0·042</td>
<td>0·207***</td>
<td>-0·159</td>
<td>0·144</td>
<td>0·004</td>
<td>0·317***</td>
</tr>
<tr>
<td>Growth: from 2 years to 11 years</td>
<td>0·689***</td>
<td>0·469***</td>
<td>0·071</td>
<td>0·459***</td>
<td>0·049</td>
<td>-0·227**</td>
<td>0·140</td>
<td>0·250***</td>
</tr>
<tr>
<td>BMI</td>
<td>0·180***</td>
<td>0·018</td>
<td>0·038</td>
<td>0·019</td>
<td>0·013</td>
<td>-0·105</td>
<td>0·041</td>
<td>0·066</td>
</tr>
<tr>
<td>Growth: from 0 to 6 months</td>
<td>0·170***</td>
<td>0·048</td>
<td>0·021</td>
<td>0·039</td>
<td>-0·061</td>
<td>0·044</td>
<td>0·080</td>
<td>0·140</td>
</tr>
<tr>
<td>Growth: from 6 months to 2 years</td>
<td>0·375***</td>
<td>0·200***</td>
<td>-0·012</td>
<td>0·209***</td>
<td>-0·095</td>
<td>-0·237***</td>
<td>0·044</td>
<td>0·256***</td>
</tr>
<tr>
<td>Growth: from 2 years to 11 years</td>
<td>0·696***</td>
<td>0·433***</td>
<td>0·057</td>
<td>0·421***</td>
<td>0·083</td>
<td>-0·175</td>
<td>0·119</td>
<td>0·265***</td>
</tr>
</tbody>
</table>

HOMA-IR, homeostasis model assessment of insulin resistance.

*** P < 0·001.

† Analyses are adjusted for sex and age at clinic visit. All measurements are in standardised form, i.e. for a standardised score, a value of 0 corresponds to the mean and a value of 1 corresponds to 1 SD above the mean and so on.
Blood pressure

Systolic and diastolic blood pressure analyses revealed similar findings, but relationships were stronger with systolic blood pressure which is presented here. Systolic blood pressure in children was directly related to first trimester maternal weight (Table 2). This association of systolic blood pressure with maternal weight was no longer statistically significant following adjustment for waist circumference measured at clinic (Table 3). It was strongly associated with height, weight and BMI during childhood (Table 4, Fig. 1(d)).

Comparison of effects in boys and girls

The results for birth weight on blood glucose and systolic blood pressure are shown in Table 5. Systolic blood pressure was inversely related to birth weight in boys, but directly

<table>
<thead>
<tr>
<th>Table 5. Multivariate regression analyses showing the systolic blood pressure and fasting blood glucose of 296 Afro-Jamaican children according to birth weight and sex (Mean values and standard deviations)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
</tr>
<tr>
<td>&lt; 3·00</td>
</tr>
<tr>
<td>3·00–3·49</td>
</tr>
<tr>
<td>≥ 3·50</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
</tr>
<tr>
<td>P for trend†</td>
</tr>
<tr>
<td>P for difference in trend</td>
</tr>
</tbody>
</table>

* Adjusted for age at clinic visit.
† Adjusted for age at clinic visit and waist circumference.
associated in girls. Similar directions of association occurred for glucose concentration.

Discussion

These data suggest that there is a developmental contribution to cardiovascular risk factors in these peri-pubertal children. They add new detail about the influence of maternal anthropometry in pregnancy and fetal and childhood growth on risk factors for CVD. Our data are unique in having multiple sequential measures of maternal anthropometry and blood pressure, placental and fetal growth, and infant and child growth through to adolescence. Most published data come from cross-sectional studies or from cohorts that cover a subset of these phases.

The girls were larger than the boys as they had progressed further through puberty at the clinic visit. These differential rates of sexual maturation may explain some of the differences in anatomy and physiology, as puberty is associated with insulin resistance due to increases in growth hormone, cortisol and insulin-like growth factor-I levels. The metabolic syndrome is associated with greater waist circumference, higher blood pressure, lower HDL-cholesterol and reduced insulin sensitivity.

We used waist circumference as the measure of current size because it is the most consistent anthropometric marker of insulin resistance even in children. Waist circumference in children was positively correlated with the size of the mother, fetus and newborn. This might simply be a consequence of the size of the child. On the other hand, more rapid growth in childhood could be associated with central adiposity. Unfortunately, we do not have measurements of segmental body composition using either MRI or dual-energy X-ray absorptiometry, so this question remains unresolved.

Glucose tolerance was maintained. There was an inverse association of glucose concentration with birth weight in boys, but a positive association in girls. Because more of the girls had advanced into puberty, the expected fetal programming effect, present in the boys, may have been obscured in the girls. Fasting plasma insulin was higher in girls, even allowing for their BMI and body composition. This might also be explained on the basis of earlier puberty (an insulin-resistant state), or conversely that girls may be intrinsically more insulin resistant.

We had expected HDL-cholesterol concentration to be directly related to placental and birth weight. However, the association was inverse. This seems to be explained by their common link with high child waist circumference.

The major determinant of systolic blood pressure was size in childhood, which was itself linked to maternal size. Again, girls and boys behaved differently. These differences in the directions of associations might also be explained on the basis of earlier puberty in girls.

Our data are consistent with the concept that the nutritional status of mothers (as reflected by their anthropometry during pregnancy) influences the risk in their offspring of increased visceral fat (as reflected by the waist circumference). This increased visceral adiposity might directly result in insulin resistance and higher blood pressure, since the associations disappear when the data are adjusted for waist circumference. Visceral adipocytes secrete many inflammatory cytokines (for example, TNF, IL-6), NEFA, as well as induce hypoadiponectinaemia, and all these factors can increase insulin resistance. It is not clear how visceral adiposity can increase systolic blood pressure, but increased production of leptin, angiotensinogen, NEFA, reactive oxygen species and adipocytokines could be causal.

Maternal size and body composition could influence the offspring’s visceral adiposity in two ways. First, maternal size may be related to the maternal hypothalamic–pituitary–adrenal axis activity. In a thin, undernourished woman, the relatively hypercortisolaemic intra-uterine environment that the fetus is exposed to results in a resetting of the fetal hypothalamic–pituitary–adrenal axis, leading to increased ambient cortisol levels ex utero. Second, larger mothers may have increased nutrient flux, as they are known to have higher insulin-like growth factor-I levels in late pregnancy. Insulin-like growth factor-I can induce greater trans-placental NEFA, glucose and lactate transfer and thus increase the number of adipocyte cells in the offspring. Subsequent exposure to a high-fat energy-dense diet would increase the risk of adiposity, insulin resistance and systolic blood pressure. Alternatively, our data cannot exclude the possibility that genetic factors influencing attainment of body size and cardiovascular risk factors may also be contributing to the variance of the observed associations. At present, these risk alleles are thought to only contribute a small amount to the variance.

It is well recognised that the major determinant of newborn size is maternal nutritional status, as measured by height, weight, weight gain, BMI and dietary intake. We therefore infer that maternal anthropometry contributes not only to fetal and newborn size but also to childhood size, and thus to the physiological correlates of insulin sensitivity, lipids and blood pressure. Thus, the maternal nutritional influence on fetal, neonatal and childhood growth, as well as the sexual maturation difference in boys and girls, are the major determinants of size, body composition and the physiological correlates. While it is not clear if traditional cardiovascular risk factors in children have the same weight or effect size as one would expect in adults, it is clear that these risk factors can track throughout life and may therefore have some impact in later life. Our data provide evidence for this biologically plausible possibility, although we cannot quantify the magnitude of the effect.

The fundamental mechanism underlying the developmental determination of risk is thought to be epigenetic modification of the fetal genome, due mainly to the effects of the maternal environment during pregnancy. Such modifications are induced by maternal nutritional and hormonal environments during peri-conception and gestation. Modification may also occur during infancy when the baby remains developmentally plastic. These functional epigenomic changes have the capacity to modify cellular, organ and whole-body metabolism, whole-body physiology and, ultimately, anatomy. Individuals whose phenotype fits them to their environments have greater likelihood of reproductive fitness, longevity and good health. In the event of a mismatch between the individual and his environment, the risk of adiposity and CVD
would be the product of epigenetically induced susceptibility and exposure.

In summary, in this cohort of Afro-Caribbean children, maternal anthropometry during pregnancy, fetal size, and childhood growth rate, contribute independently to cardiovascular risk factors in childhood.

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T. E. F. contributed to all stages of the study (study design, data collection, analysis and interpretation of the data, and writing of the manuscript) and developed the first draft of the manuscript. M. S. B. contributed to the study design, data collection, interpretation of the data and the writing of the manuscript. C. O., R. A. F. and M. R. contributed to the data analysis and the writing of the manuscript. C. T.-B. and S. S.-W. contributed to data collection and writing of the manuscript.

None of the authors has any conflict of interest.

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