Association of growth *in utero* with cognitive function at age 6—8 years

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Abstract

**Background:** Size at birth is associated with later cognitive development. The timing of growth faltering *in utero* may affect developmental consequences.  
**Aim:** To determine whether growth *in utero* is related to cognitive outcomes in childhood. A secondary aim was to determine any associations between maternal nutritional status and cognition.  
**Study design and subjects:** Subjects were participants in a prospective cohort study of developmental origins of adult disease. Eligible subjects were aged 6—8 years at their next scheduled visit to the study clinic and their mothers had abdominal ultrasound measurements at 14, 25 and 35 weeks gestation. 186 of 264 eligible children attended the clinic and were tested.  
**Outcome measures:** Raven’s Progressive Matrices (reasoning ability), Peabody Picture Vocabulary Test (receptive vocabulary) and Digit Span Forwards (auditory working memory).  
**Results:** In multiple regression analyses controlling for children’s age and socioeconomic status, head circumference at 14 weeks gestation was significantly associated with reasoning ability. The difference between the lowest and highest quartiles was equivalent to 0.4 S.D. No other significant associations with fetal growth were found. Maternal weight gain was not associated with cognitive scores; however, change in triceps skinfold between 25 and 35 weeks gestation was positively associated with reasoning ability and remained a significant predictor when included in the regression model.  
**Conclusions:** There were few associations between growth *in utero* and cognition. Growth in head circumference in early gestation and maternal nutrition in late gestation may affect later cognitive ability. Further research in this area is needed to confirm these results.

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1. Introduction

Associations between birth weight and later cognitive and behavioural deficits have been reported in both developed [1,2] and developing countries [3—5], with associations continuing within the normal birth weight range [6,7].

The timing of growth faltering in utero may affect the nature or magnitude of developmental consequences. Studies in which low ponderal index was used as a proxy for growth restriction in late pregnancy have had inconsistent results [1,4,8,9]. Serial ultrasound measurements provide a more direct measure of fetal growth; however, we are aware of only two studies with serial ultrasound measures in which later cognitive function was assessed [10,11]. Faltering in head growth before 26 weeks gestation was associated with poorer developmental levels at age 5 years but faltering after 26 weeks did not affect development [10]. Growth in abdominal circumference in the third trimester was not related to development at age 1 year [11]. Although the samples were small, these studies suggest that later cognitive development may be more closely associated with early fetal growth than with later growth.

Maternal nutritional status is associated with infant size at birth [12] and has been shown to have later functional consequences for offspring [13]. There is little information relating maternal nutritional status to cognitive outcomes. Early pregnancy weight and micronutrient status predicted infant behaviour and development [14,15]; however, in another study, children of mothers with high pre-pregnancy weight and micronutrient status could confound any associations seen with fetal growth.

In November 1992, a study of the maternal determinants of fetal and placental growth was initiated and a cohort of infants established in whom issues related to developmental origins of adult disease are being investigated [17]. Repeat- ed measurements of growth in utero by ultrasound and maternal anthropometry were made as well-detailed an- thropometry at birth [18]. This cohort thus provides the opportunity to begin to explore any associations of growth rates in utero with cognitive outcomes. We hypothesized that slower fetal growth, particularly measures of head growth, might reflect brain growth and development and thus be related to later cognitive performance. A secondary aim was to determine any association between maternal nutritional status and cognitive function. Maternal nutritional status could be associated with outcomes in the offspring through effects on fetal growth and through alterations in the in utero environment even where growth is unaffected. We also determined any association of birth size and postnatal anthropometry with cognitive outcomes as such associations have been reported in other studies and could confound any associations seen with fetal growth.

2. Participants and methods

The subjects were members of an ongoing cohort study of developmental origins of adult disease [17] whose mothers had been recruited at their first antenatal clinic visit to the University Hospital of the West Indies, Kingston, Jamaica. Recruitment was restricted to women who were aged between 14 and 41 years, were sure of the dates of their last menstrual period, and who did not have systemic illnesses or genetic abnormalities (e.g., sickle cell disease). Details of subject recruitment have been reported previously [18]. Five hundred and thirty-two women completed the study up to delivery and agreed to participate in a longitudinal study of postnatal growth and blood pressure. Of this cohort, 264 children aged between 6 and 8 years whose mothers had ultrasound measurements at 14, 25 and 35 weeks gestation and who continued to attend the follow-up clinic were eligible for this study.

Testing was done at the children’s regular six monthly visits to the follow-up clinic at the Tropical Metabolism Research Unit. Informed consent was obtained from the child’s parent/guardian. Testing was conducted over a 6-month period from April to September 2002 during which all the children had a scheduled visit. One hundred and eighty-six eligible children (84 boys, 102 girls mean age 7.5 SD 0.8 years) attended the clinic during the study period and were tested. The children who were tested were not different from the rest of the cohort enrolled at birth in birth weight. A socioeconomic status (SES) score on enrollment was computed from crowding, household possessions, toilet and water facilities, mothers’ and fathers’ education and occupation and maternal post-school training. This SES score was slightly lower in those who were tested than in the rest of the cohort (p < 0.05).

Ethical approval for the study was obtained from the Ethics Committee of the University of the West Indies.

2.1. Cognitive tests

Three tests of the children’s cognitive ability were used. Reasoning ability was measured with the Raven’s Progressive Matrices [19], language comprehension with the Peabody Picture Vocabulary Test [20] and auditory working memory with Dgit Span Forwards (a subtest of the Wechsler Intelligence Scales). These measures have been used previously in Jamaica, are reliable in this population and have been sensitive to differences in post-natal nutrition [21]. A single observer tested all the children. Inter-observer agreement between the trainer and tester before beginning the study was > or =99% (n=20). The trainer observed 9% of test sessions and the same level of agreement was maintained.

2.2. Fetal growth

Abdominal ultrasound measurements (linear probe, ATL Ultramark IV, [18]) of head circumference, biparietal diameter, femoral length, abdominal circumference at 14, 25 and 35 weeks of gestation were used as measures of fetal growth in early, mid- and late gestation. The reliability of ultrasound measurements within and between two trained observers was assessed in 20 subjects before the study began. Intra-class correlation coefficients ranged from 0.992 to 0.995. Reliability was reassessed at three monthly intervals throughout the study and remained high.

2.3. Size at birth and postnatal growth

Weight, head circumference, and crown heel length at birth were measured according to standard procedures and ponderal index calculated. Gestational age was determined
by the date of the last menstrual period (LMP), validated by ultrasound scan at 14 weeks of gestation. Women were excluded from the study if they were unsure of the date of the LMP or the estimates of gestational age did not agree. Weight, length and head circumference at 6,12 and 24 months of age were used as measures of early postnatal growth, and these measurements were also obtained at the follow-up visit when the children’s cognitive function was assessed.

2.4. Maternal anthropometry

Mother’s weight, height and triceps skinfold thickness were measured at each antenatal clinic visit using standard techniques. Pre-pregnancy body mass index was calculated using weight at the first visit (7–10 weeks gestation).

2.5. Maternal and social background characteristics

Information on maternal and social background characteristics was obtained on initial recruitment (housing, maternal education and occupation). This information was collected again by brief interview at the time of the cognitive tests and additional information was obtained on family structure. Summary scores of the number of possessions and the level of crowding (number of persons per room) were calculated.

2.6. Statistical analysis

The standardized residuals of regressions of the fetal measurements (biparietal diameter, femoral length, and head and abdominal circumference) on gestational age at measurement were used to adjust for variation in the gestational age at measurement. Partial correlation coefficients controlling for the children’s age at testing were calculated between the residual for each measurement at the three time points (14, 25 and 35 weeks gestation) and the cognitive scores. Further analyses were conducted only where the residuals were significantly correlated with cognitive scores. Multiple regression analyses were conducted predicting the cognitive test scores from the residuals as continuous variables. Analyses were also conducted with the residual divided into quartiles to determine the magnitude of the difference in Raven’s scores between children at either end of the distribution. All analyses were adjusted for age and mothers’ occupation which was the social background variable with the strongest association with the cognitive scores in preliminary univariate analyses. Two dummy variables were used comparing mothers whose occupations were skilled or highly skilled/professional with the reference category of unskilled/semi-skilled.

A similar approach was used to determine any associations between the cognitive scores and maternal nutritional status (weight and BMI at first antenatal visit, weight gain and change in triceps skinfold thickness), birth size, size at 6, 12, 24 months, and current size. Partial correlation coefficients controlling for the children’s age at testing were calculated and then multiple regression analyses conducted only with variables with significant associations with the cognitive scores in the preliminary analyses.

Residuals from regressions of later measurements of weight or triceps skinfold on measurements earlier in gestation were used as measures of change. For weight gain, the exact length of the interval between the measurements was included in the regressions. Analyses were conducted with SPSS for WINDOWS version 11.5 (SPSS Inc. Chicago, IL).

3. Results

The mean birth weight of the children was 3.19 kg (S.D. 0.46) and mean gestational age was 39.7 weeks (S.D. 1.3). Ninety-seven percent of the Jamaican population is of West African descent [22]. Previous studies suggest that infants born to parents of African origin have birth weights of approximately 3.1 kg, 150–200 g below those of a Caucasian comparison group [23,24]. The infants in this study were therefore of average size for an African origin population and only 7.6% were low birth weight, with weights ranging from 2000 to 2480 g. All except 7 children were born at term (≥37 weeks), and these seven were born between 35.9 and 36.9 weeks gestation. About half of the children were first-born (49.5%). The participants’ height-for-age and BMI-for-age z-scores were calculated using the CDC references [25]. The population averages were close to the reference mean and few children were undernourished. (Height-for-age z-score mean (S.D.): at 24 months 0.46 (0.92); current study 0.57 (0.93). BMI-for-age z-score mean (S.D.): at 24 months 0.39 (1.05); current study 0.24 (1.33).

The average age of the mothers was 27.7 years, with only one mother younger than 18 years and another six 18–19 years. Sixteen mothers were aged 35 years or older. The mean pre-pregnancy BMI of the mothers was 24.5 kg/m² (S.D. 5.0), indicating that they were generally a well-nourished population. Seven percent of the sample was underweight as defined by BMI < 18.5 and 15% were obese (BMI ≥ 30). Overweight and obesity is common among Jamaican women [26]. The sample was predominantly low income to low-middle income and contained few very poor or very affluent families. The majority of the mothers (60.8%) had not passed any secondary level examinations and most worked in semi-skilled or skilled occupations (29.1% and 41.8%). Fifty-two percent of the children currently lived with both their parents.

There were no significant differences in the children’s cognitive test scores by gender. The mean scores were Digit Span 7.1 (S.D. 1.4) Peabody Picture Vocabulary Test 59.2 (S.D. 16.6) and Raven’s Matrices 17.1 (S.D. 4.1).

The partial correlation coefficients between the children’s scores on the Raven’s Matrices and head circumference at 14 weeks (r = 0.17, p = 0.022), and abdominal circumference at 25 weeks (r = 0.16, p = 0.033), were significant. There were no significant correlations between the measurements of growth in utero and scores on the PPVT or digit span forwards. Further analyses were therefore restricted to the Raven’s scores and head circumference at 14 weeks, and abdominal circumference at 25 weeks.

The residuals were divided by quartiles to illustrate the range in test scores between those at the lower and higher ends of the distribution. The scores varied among the quartiles for head circumference (Table 1), but the differences were reduced after adjustment for the children’s
age. The analysis for abdominal circumference was not significant.

Multiple regression analyses were conducted to examine the association of head circumference and the Raven's test scores adjusting for age and maternal occupation. Two regressions were conducted. In the first, the residual for head circumference at 14 weeks was entered as a continuous variable, and in the second, dummy variables for the quartiles were used with the last quartile as the reference. Head circumference at 14 weeks was significantly associated with reasoning ability at age 6–8 years with the difference between the lowest and highest quartiles being significant (Table 2). A quadratic term for the residual for head circumference at 14 weeks was also offered in the regression with the continuous variable but was not significant.

To determine whether fetal growth after 14 weeks modified the effects of head circumference at 14 weeks, two further regressions were conducted entering the head circumference residuals at 14 and 25 weeks and at 14 and 35 weeks. The later residuals were not related to the Raven's scores and their inclusion resulted in little change in the regression coefficient for head circumference at 14 weeks which was still significantly associated with the test scores.

The only significant correlation between the Raven's scores and size at birth was with birth weight (partial correlation controlling for gestational age, \( r = 0.20 \), \( p < 0.05 \)); however, birth weight was not a significant predictor of the Raven's score when included in the regression model (other independent variables in the model were as described above—child's age, maternal occupation and the residual for head circumference at 14 weeks). There were no significant correlations with anthropometry at 6, 12 and 24 months of age or with current size. The 14-week ultrasound measure was significantly associated with head circumference at birth but did not predict later head size.

Maternal weight and BMI in early pregnancy were not associated with the children's cognitive scores. There were also no significant differences when the mothers were categorized by BMI as underweight, normal weight, overweight or obese. Weight gain was also not significantly associated with the cognitive scores. Change in triceps skinfold from 25 to 35 weeks gestation was positively correlated with the children's scores on the Raven's test (\( r = 0.15 \), \( p < 0.05 \)) and remained a significant predictor when included in the regression model (Table 3). In this final model, the percent of variance in the Raven's score associated with the 14-week head circumference and change in triceps skinfold was 1.5% and 1.9%. This compares to 11.5% due to social background as measured by mother's occupation.

### 4. Discussion

We found little association between fetal growth measured by ultrasound and cognitive function in childhood. The only significant association was between head circumference in early gestation and reasoning ability with a difference between the lowest and highest quartile equivalent to 0.4 S.D. The average scores for reasoning ability in the study children were equivalent to the 25th percentile for the reference population in the UK [19]. The lower scores than those for the reference population are possibly due to the study sample being predominantly lower to lower—middle income. The average score of children in the lowest quartile for fetal head growth would be classified as below

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Unadjusted and age-adjusted scores on the Raven’s Matrices by quartile of head circumference at 14 weeks</th>
</tr>
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<tbody>
<tr>
<td>Quartile</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>15.6</td>
</tr>
<tr>
<td>2</td>
<td>17.0</td>
</tr>
<tr>
<td>3</td>
<td>17.6</td>
</tr>
<tr>
<td>4</td>
<td>18.1</td>
</tr>
<tr>
<td>( p^b )</td>
<td>0.013</td>
</tr>
</tbody>
</table>

\( ^a \) CI: confidence interval.
\( ^b \) ANOVA, children's age as covariate in age-adjusted analyses.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Regression coefficients (8) and standard error (S.E.) from multiple regressions of Raven's Matrices score on head circumference at 14 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( B )</td>
</tr>
<tr>
<td>1. Head circumference at 14 weeks</td>
<td>0.59</td>
</tr>
<tr>
<td>2. Quartiles of head circ. at 14 weeks (highest quartile is reference group)</td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>-1.59</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>-0.88</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>-0.72</td>
</tr>
</tbody>
</table>

Children's age and caretakers' occupation were significant covariates in both regressions. In Regression 1, the standardized residual of head circumference at 14 weeks on gestational age at measurement is used and in regression 2 dummy variables for the residual grouped by quartiles.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Regression coefficients (8) and S.E. (standard error) from multiple regression of Raven's Matrices score on head circumference at 14 weeks and change in maternal triceps skinfold from 25 to 35 weeks gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( B )</td>
</tr>
<tr>
<td>Child's age (years)</td>
<td>1.60</td>
</tr>
<tr>
<td>Change in maternal triceps skinfold</td>
<td>0.56</td>
</tr>
<tr>
<td>Head circ. at 14 weeks ( ^b )</td>
<td>0.64</td>
</tr>
<tr>
<td>Caretaker's occupation ( ^a )</td>
<td>1.01</td>
</tr>
<tr>
<td>Skilled</td>
<td>4.15</td>
</tr>
<tr>
<td>Highly skilled/professional</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Reference category—Unskilled/semiskilled.
\( ^b \) Standardized residual of head circumference at 14 weeks on gestational age at measurement.
\( ^c \) Standardized residual of triceps skinfold at 35 weeks on triceps skinfold at 25 weeks.
average, while those in the higher quartiles would be within the average range. In one previous study, slower head growth was related to later development only where this occurred prior to 26 weeks gestation [10]. In that study, biparietal diameter was first measured at 20–24 weeks gestation, whereas in our study measurements were obtained at 14 weeks gestation and we found a relationship between head circumference in early gestation and later obtained at 14 weeks gestation and we found a relationship between head circumference in early gestation and later cognition. We are aware of only one other study [11] in which the relationship of fetal growth, using ultrasound measures, and later cognitive ability has been examined and the findings from the present study need replication.

We were able to assess only 35% of the cohort enrolled at birth. Children tested tended to be of lower socio-economic background than those not tested. However, they did not differ in birth weight and the 14-week head circumference was not correlated with socioeconomic background. It is therefore unlikely that loss to follow-up had any substantial effect on the results.

We looked at three cognitive tests and relationships were found only between reasoning ability and early head circumference. No associations were found between fetal growth and the children’s receptive vocabulary (PPVT) or auditory working memory. Thus, the possibility that the measurement may be a useful indicator of maternal energy status.

Maternal nutritional status has been related to the cognitive and behavioural development of their offspring in few studies and most have focused on specific micro-nutrients or essential fatty acids [14,15,29,30]. There is little information on the importance of maternal body composition and energy balance for later development. Our findings suggest that a more positive maternal energy balance in late gestation, as reflected by the change in triceps skinfold thickness between 25 and 35 weeks gestation, is associated with better reasoning ability in childhood. The mechanism remains to be clarified. Maternal triceps skinfold during gestation has been associated with other functional outcomes [31,32] which suggests that this measurement may be a useful indicator of maternal energy status.

Birth weight was associated with reasoning ability, but we found no other associations between size at birth or during childhood with the cognitive test scores. Several studies have shown associations between poor growth in childhood and later cognitive outcome [33,34]. Few of the children in the present study were low birth weight (and all were ≥2000 g) and their postnatal growth was good, and this may explain the lack of association between postnatal size and cognition. Although associations between height and cognition in well-nourished populations have been reported, the findings are less consistent and the correlations usually only modest [35–37].

This study provides the largest sample to date in which associations between ultrasound measures of fetal growth and later cognitive function have been assessed. A significant association was found between early fetal head growth and reasoning ability at age 6–8 years, but there were no other significant associations between fetal growth and childhood cognition. Few of the children in this study experienced significant growth retardation in utero or postnatally. The results might be different in growth-retarded infants and children. Further research in this area is needed to confirm these results.

Acknowledgements

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References


