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Growth in utero and cognitive function in adult life: follow up study of people born between 1920 and 1943

Christopher N Martyn, Catharine R Gale, Avan Aihie Sayer, Caroline Fall

Abstract
Objectives—To examine the relation between fetal growth and cognitive function in adult life.

Design—A follow up study of men and women whose birth weights and other measurements of body size had been recorded at birth.

Setting—Hertfordshire, Preston, and Sheffield.

Subjects—1576 men and women born in Hertfordshire, Sheffield, or Preston between 1920 and 1943.

Main outcome measures—Intelligence quotient as measured by the AH4 test and amount of decline in cognitive function with age as estimated by the difference between score on the Mill Hill vocabulary test and score on the AH4 test.

Results—Score on the intelligence test was higher in people who had a large biparietal head diameter at birth, but it was not related to any other measure of body size or proportions. No association was found between decline in cognitive function and any measure of size or proportions at birth.

Conclusion—Impaired fetal growth was not associated with poorer cognitive performance in adult life. Adaptations made by the fetus in response to conditions that retard its growth seem to be largely successful in maintaining brain development.

Introduction
There is considerable evidence that malnutrition in early life can have an adverse effect on the developing brain.1 During various critical periods in the development of the central nervous system, malnutrition has been shown to affect the morphology, physiology, and neurochemistry of the brain, and this may have important implications for future cognitive function.2,3 Undernutrition during proliferative growth of the brain, for example, retards the rate of cell division and causes a permanent reduction in numbers of brain cells.4 Animal studies suggest that such nutritional privation during fetal life affects later performance on tests of learning.5 In humans, low birth weight and proportionate smallness at birth, both of which may result from undernutrition in utero, have been associated with poorer performance on tests of cognitive function in early childhood.6,7 There have been few studies, however, on whether poor fetal growth has a lasting effect on adult cognitive performance.

In several community surveys of older people, cognitive function has been assessed by using the AH4 intelligence quotient (IQ) test and the Mill Hill vocabulary test.8 Studies have shown that cognitive skills do not all deteriorate at the same rate.9 10 The AH4 test provides a measure of fluid intelligence, which tends to decline with advancing age, while score on the Mill Hill vocabulary test gives an estimate of crystallised intelligence, which may be retained unimpaired until very late in life.11 By measuring the discrepancy between scores on the two tests an indication of the amount of decline in cognitive ability can be obtained.12 We studied the cognitive performance of older men and women who had been measured in unusual detail at birth. We investigated whether intrauterine growth was related to adult intelligence. Because we thought it possible that the rate of cognitive decline with age might be influenced by growth in utero, we also investigated whether early measurements were associated with the discrepancy between score on the Mill Hill vocabulary test and score on the AH4 IQ test.

Subjects and methods
From 1911 onwards each child born in Hertfordshire was seen immediately after birth by a health visitor and its birth weight was recorded in centrally held registers. In Preston and Sheffield a standardised record was kept for each woman admitted to the labour wards at Shore Green Hospital and Jessop Hospital for Women, respectively. These records included details of the baby's birth weight, length from crown to heel, and measurements of abdominal circumference, head circumference, biparietal diameter, and occipitofrontal diameter. The NHS central register was used to trace singleton infants born to married mothers in Hertfordshire, Preston, and Sheffield. Those who were still living in the area of their birth were invited to take part in various studies into the processes by which the environment in early life influences adult disease.13 14

In this analysis we used five datasets comprising men and women who still lived in the area in which they were born. Subjects were invited to participate and were interviewed if they agreed. They were then invited to undergo psychometric testing. Table 1 gives details of the participants.

Subjects took part 1 of the AH4 IQ test, which provides a measure of logical, verbal, and numerical reasoning, and the Mill Hill vocabulary test. To obtain an estimate of the amount of decline in cognitive function, we standardised the scores on the two tests using Z scores and calculated the difference between them.15 16

We analysed all the datasets together, with multiple linear regression and tabulation of means to examine the relation between measurements of body size at birth, score on the AH4 intelligence test, and amount of change in cognitive function. Birth weight, length, ponderal index, and head circumference were divided into

Table 1—Details of participants and response rates

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Sex</th>
<th>Birth place</th>
<th>Years</th>
<th>No invited to participate</th>
<th>No (%) interviewed</th>
<th>No (%) who took test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Woman</td>
<td>East Hertfordshire</td>
<td>1920-30</td>
<td>565</td>
<td>388 (69)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Men and women</td>
<td>North Hertfordshire</td>
<td>1920-30</td>
<td>1428</td>
<td>824 (58)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Men and women</td>
<td>Preston</td>
<td>1935-43</td>
<td>393</td>
<td>266 (68)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Men and women</td>
<td>Sheffield</td>
<td>1939-40</td>
<td>419</td>
<td>327 (80)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Men and women</td>
<td>Sheffield</td>
<td>1922-6</td>
<td>513</td>
<td>322 (63)</td>
</tr>
</tbody>
</table>

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MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD
Christopher N Martyn, clinical scientist
Catharine R Gale, research student
Avan Aihie Sayer, Welcome research fellow
Caroline Fall, clinical scientist

Correspondence to:
Dr Martyn.
Table 2—Mean birth measurements, age, and score on psychometric tests. All figures are means (SD)

<table>
<thead>
<tr>
<th>Detail</th>
<th>All areas (n = 1576)</th>
<th>Herts 1 (n = 295)</th>
<th>Herts 2 (n = 694)</th>
<th>Preston (n = 107)</th>
<th>Sheffield 1 (n = 227)</th>
<th>Sheffield 2 (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth measurement*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (oz)</td>
<td>119.3 (18.5)</td>
<td>121.3 (19.2)</td>
<td>121.9 (17.8)</td>
<td>109.5 (18.6)</td>
<td>114.6 (17.8)</td>
<td>117.8 (18.3)</td>
</tr>
<tr>
<td>Length (in)</td>
<td>20.1 (1.1)</td>
<td>—</td>
<td>—</td>
<td>20.2 (1.1)</td>
<td>19.9 (1.0)</td>
<td>20.2 (1.1)</td>
</tr>
<tr>
<td>Ponderal index (oz/in²)</td>
<td>14.2 (1.9)</td>
<td>—</td>
<td>—</td>
<td>13.2 (1.6)</td>
<td>14.5 (1.7)</td>
<td>14.3 (2.0)</td>
</tr>
<tr>
<td>Head circumference (in)</td>
<td>13.6 (0.7)</td>
<td>—</td>
<td>—</td>
<td>13.6 (0.8)</td>
<td>13.5 (0.7)</td>
<td>13.6 (0.7)</td>
</tr>
<tr>
<td>Occipitofrontal diameter (in)</td>
<td>4.5 (0.4)</td>
<td>—</td>
<td>—</td>
<td>4.4 (0.3)</td>
<td>4.5 (0.5)</td>
<td>4.4 (0.3)</td>
</tr>
<tr>
<td>Biparietal diameter (in)</td>
<td>3.6 (0.4)</td>
<td>—</td>
<td>—</td>
<td>3.5 (0.2)</td>
<td>3.7 (0.5)</td>
<td>3.5 (0.3)</td>
</tr>
<tr>
<td>Abdominal circumference (in)</td>
<td>12.3 (1.1)</td>
<td>—</td>
<td>—</td>
<td>12.4 (1.1)</td>
<td>12.2 (1.1)</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.9 (2.1)</td>
<td>53.6 (3.0)</td>
<td>67.1 (3.3)</td>
<td>53.2 (3.3)</td>
<td>52.1 (0.6)</td>
<td>68.6 (1.4)</td>
</tr>
<tr>
<td>AH4 score</td>
<td>22.5 (9.2)</td>
<td>21.2 (10.2)</td>
<td>22.1 (9.2)</td>
<td>25.4 (8.2)</td>
<td>24.8 (8.3)</td>
<td>21.6 (9.1)</td>
</tr>
<tr>
<td>Mill Hill score</td>
<td>18.0 (4.7)</td>
<td>17.0 (4.8)</td>
<td>18.0 (4.8)</td>
<td>19.1 (4.0)</td>
<td>18.7 (4.2)</td>
<td>18.2 (5.0)</td>
</tr>
<tr>
<td>Decline in cognitive function</td>
<td>0.03 (0.8)</td>
<td>0.04 (0.8)</td>
<td>0.04 (0.8)</td>
<td>-0.04 (0.9)</td>
<td>-0.01 (0.9)</td>
<td>0.04 (0.2)</td>
</tr>
</tbody>
</table>

*All measurements are given as originally recorded; 1 oz=28 g. 1 inch=2.5 cm.

Discussion

In these data there were few associations between fetal growth and adult cognitive function. No relation was found between any measure of body size or proportions at birth and adult intelligence, with the exception of biparietal diameter. People with a large biparietal diameter at birth tended to gain higher scores on the
AH4 IQ test. No associations were found between decline in cognitive function related to age and either size or proportions at birth.

Our results are based on 1576 subjects who took the two psychometric tests. This is 47% of those originally invited to participate. Furthermore, the participants are unrepresentative of all people born in Hertfordshire, Sheffield, or Preston because they have continued to live in the area of their birth. All comparisons, however, have been made within the study sample. Unless the relations between birth measurements and cognitive function in adult life differ in non-responders or in people who have died or moved away, no bias will have been introduced.

Measurements of head circumference correlate closely with brain size at birth. A small head circumference at one year has been associated with a lower score on intelligence tests in early childhood. We found a significant association between biparietal diameter at birth and score on the AH4 IQ test in adult life, but this is hard to interpret in the absence of any association with other measurements of head size; it may be due to chance.

GROWTH RETARDATION IN GESTATION

Babies who have been exposed to chronic nutritional deprivation from the early stages of pregnancy may be proportionately small at birth, showing signs of growth retardation in all dimensions including head size. Such babies are more prone to neurodevelopmental impairment. A follow up study of small for dates babies found that those who had experienced an early onset of failure of growth in utero had a lower score on tests of cognitive development at the age of 4 years. Several studies have reported that babies who are proportionately small at birth, with growth retardation in both weight and length, show signs of impaired intellectual development in the first years of life. In contrast, when growth retardation occurs in mid or late gestation, head circumference and brain growth tend to be spared. One mechanism for this involves cardiovascular adaptations that maintain blood flow to the brain at the expense of the trunk. Babies who have experienced this sort of growth retardation may be identified by a raised ratio of head circumference to abdominal circumference. Follow up studies of babies with growth failure in the later stages of pregnancy found no evidence of impaired intellectual development in early childhood. Babies who were exposed to the Dutch famine of 1944-5 during the third trimester of pregnancy were found to be growth retarded in weight and to a lesser extent in length and head circumference. But when men born during this period were given a series of psychometric tests, no association was found between mental performance and prenatal exposure to famine.

We examined the relation between mental performance and body proportions at birth but found no significant associations between AH4 score and either ponderal index, ratio of head circumference to length, or ratio of head circumference to abdominal circumference. AH4 score was higher with increasing birth weight, but this trend was not significant. The fact that we found no relation between growth in utero and cognitive performance may be related to the age of our subjects. They were born during a period when the survival chances of infants with a low birth weight or growth retardation were much smaller than today, and there may have been too few such babies among our subjects to detect any difference in cognitive function. An alternative explanation for our findings is that most of the growth retardation in our subjects occurred in mid or late gestation, when fetal redistribution of blood circulation allows preferential flow to the brain. Poor growth in fetal life, however, is only one of several potential factors which may inhibit brain development.

Parent-child relationships, the quality and amount of intellectual stimulation, and the socioeconomic environment into which the baby is born are all likely to operate synergistically to influence cognitive development. Undernutrition in infancy and early childhood has been associated with poor mental function, though only in the presence of a lack of social and intellectual stimulation. By the time the baby reaches adulthood, environmental factors in postnatal life may overshadow any effect of intrauterine experience on cognitive performance.

Many of the causes of cognitive decline in later life are still unclear. There are clear individual differences in the rates at which cognitive function changes with age, and only some of this variation can be explained by the presence of pathologies known to impair mental performance. We speculated that as poor fetal growth is linked to several diseases of old age, it might be an association between cognitive decline and size at birth, but we found no significant relations with any measure of size or body proportions at birth.

CONCLUSIONS

Previous studies have found relations between birth measurements and cardiovascular disease and its risk factors. These findings have been interpreted as indicating that undernutrition and other adverse influences during critical periods in utero may permanently programme the body's structure, physiology, and metabolism, leading to an increased risk of disease in later life. We examined the cognitive function of older men and women who had been measured in unusual detail at birth to investigate whether impaired fetal growth was associated with poorer mental performance in later life, but found no strong associations. The psychometric tests used in this study do not provide a comprehensive test of cognitive abilities so there may be areas of mental function that are affected by poor growth in utero. None the less, our findings suggest that fetal growth is less important than genetic factors and environmental influences in postnatal life in determining adult cognitive performance. Adaptations made by the fetus in response to conditions that retard its growth seem to be largely successful in maintaining its brain development.

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Perioperative myocardial infarction in peripheral vascular surgery

N Mamode, RN Scott, SC McLoughlin, AM McLelland, JG Pollock

The commonest major complication in patients undergo-
ing peripheral vascular surgery is perioperative myocardial infarction.1 The commonest major complication in patients undergo-
ing peripheral vascular surgery is perioperative myocardial infarction.1 No study in Britain has prospec-
tively assessed this risk, but a recent retrospective study found an incidence of 6.3% in patients undergoing aor-
tic surgery.2 We report the incidence of perioperative myocardial infarction in our unit, which is a regional centre for peripheral vascular surgery.

Patients, methods, and results

We studied consecutive patients undergoing peripheral vascular surgery after excluding those who were under-
going surgery for trauma, venous surgery, and minor procedures. Patients thought to be at high risk of perioperative myocardial infarction were referred to a cardiologist for further preoperative assessment. Concentrations of creatin-

ine kinase MB isoenzymes were measured (by Immuno STAT). For the first three days after surgery, and electrocardiograms were recorded on admission, on discharge from hospital, and at doctors' discretion. Because the concentration of creatinine kinase MB isoen-
zyme may be raised by skeletal muscle ischaemia, myocardial
infarction was diagnosed only when a raised total creatinine kinase concentration was associated with an MB subunit concentration of >10 ng/ml and a ratio of MB

subunit to total creatinine kinase of $\geq 0.5$. Cardiac death was defined as death unequivocally related to myocardial infarction, heart failure, or arrhythmias. The primary end points of our study were myocardial infarction or cardiac death within 30 days of surgery. We performed statistical analysis with the $\chi^2$ test or, when appropriate, Fisher's exact test.

The 191 patients included in our study (128 men, median age 65, and 63 women, median age 70) underwent 204 operations, of which 100 were elective procedures, 70 were urgent (requiring surgery within the same hospital admission), and 31 were emergency surgery (requiring surgery within 24 hours). Ninety one of the operations were carried out for critical ischaemia, 32 were aortic procedures, and 120 patients (of the 182 in whom data were available) had preoperative evidence of ischaemic heart disease.

The overall incidence of perioperative myocardial infarction and cardiac death was 7.3%. Six of these were elective or urgent procedures and 12% for those undergoing emergency surgery. Table 1 gives details of the six myocar-
dial infarctions and eight cardiac deaths that occurred. Four of the non-fatal infarctions were clinically silent. Two patients had surgery performed under regional anaesthesia (amputa-
tion and brachial embolecemy), while the rest had a general anaesthetic. Three patients were submitted to necropsy, which showed subendocardial infarction in two patients and transmural infarction (probably preceding surgery) in the other. The factors associated with perioperative myocardial infarction were age over 70 ($\chi^2=4.642$, $P=0.03$), sex ($\chi^2=3.989$, $P=0.05$), perioperative shock (Fisher's exact test $\chi^2=6.949$, $P=0.05$), and angina (Fisher's exact test $\chi^2=7.317$, $P=0.008$).

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