Early Growth and Later Development

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There has been long-standing interest in whether a stimulus at a sensitive or critical period in development could have a long-lasting or permanent “programming” influence on later structure or function. For some types of cell (e.g., brain and muscle), differentiation and replication, or determination of cell function, occur only during limited critical periods of early development (1). Adverse factors during such a period, particularly those leading to growth failure, may therefore have a detrimental effect on an individual throughout life.

There has been recent epidemiological evidence that nutrition or growth in early life may influence long-term outcome in terms of later body size (2,3) and risk of adult disease (4-7). It is of concern to neonatologists that suboptimal nutrition during early life could have adverse long-term consequences for growth, health, or neurodevelopment in infants born preterm. Our randomized nutritional intervention trials have provided evidence that nutrition in the neonatal period affects growth (8,9). Neonatal steady-state weight gain (weight gain in g/kg·d after regaining birthweight) was significantly improved by feeding a nutrient-fortified preterm formula rather than either donor breast milk or a standard term formula. More important, our studies have also provided evidence that nutrition in the neonatal period can influence later performance, with improved developmental outcome at 9 and 18 months post term (9-12). Unpublished data suggest that this effect persists until the age of 7.5 to 8 years, particularly in respect to verbal IQ in boys.

Martyn et al. found no relation between fetal growth (birthweight) and adult cognitive performance among a population born between 1920 and 1943, the vast majority of whom would have been born at term (13). The brain is growing fastest around the time of full term, and it continues to grow beyond the end of the first year of life (14). Skuse et al. conducted a large study in term infants to investigate whether postnatal growth influences Bayley mental and motor scores at 15 months (15). They calculated a combined score and found no association between birthweight or weight at 15 months and Bayley combined score. However, they did find that early growth faltering was important. From regression models they found that a fall of 2 SD in weight between birth and 6 months was associated with a 10-point
deficit in developmental score, whereas the same degree of growth faltering between 4 and 10 months was associated with a 3-point deficit. Whether these early developmental deficits result in a long-term cognitive disadvantage has not been investigated.

The possibility that early growth performance per se is important for later cognitive performance has not been investigated in preterm infants. We explored these issues in a large group of children born preterm who were enrolled in parallel randomized nutritional intervention trials in the United Kingdom from 1982 to 1984 and followed up through childhood (10). We tested the hypothesis that weight gain in the neonatal period or in the first 9 months post term influences outcome at 7.5 to 8 years.

Milks routinely fed to preterm infants at that time differed substantially in nutrient content, ranging from donor breast milk (from unrelated breastfeeding mothers in the community) or a standard term formula to a nutrient-enriched preterm formula designed to meet the special nutrient needs of babies born preterm, a time of rapid growth. It was both practical and ethical to undertake a randomized trial; the results were needed for informed management decisions. Because of the large differences in nutrient content between the allocated milks, we were able to investigate, in randomized prospective intervention trials, whether early nutrition influenced later development and cognitive performance (9,11,12).

Altogether, 926 infants born weighing under 1850 g in five centers in the United Kingdom in 1982 to 1984 were randomly allocated their early enteral diet. The randomization was as shown in Fig. 1. Study 1 compared banked donor milk with the preterm formula fed either as sole diets or as a supplement to the mother’s expressed breast milk, if she could not provide enough milk to meet her infant’s needs. Study 2 compared a standard term formula with the preterm formula, again as sole diets or as a supplement to mother’s milk. The assigned diets were fed, on average, for only the first 4 weeks of life. After this period the infants were fed as their parents and medical advisers chose.

Weight was measured daily and weight gain in the neonatal period after regaining birthweight was calculated in g/kg-d. Within the population neonatal growth performance varied greatly, from 4.2 to 29.9 g/kg·d (mean 14.7, SD 3.8). Extensive social, demographic, and obstetric data were collected by trained research nurses, together with detailed prospective neonatal data, according to predefined criteria. Social class was coded into six categories (United Kingdom Registrar General’s classification) and mother’s educational attainments were coded according to categories published previously (16).

Surviving children in study 1 were weighed and measured at 9 months post term, 18 months post term, and 7.5 to 8 years of age. Those in study 2 were weighed and measured at 18 months post term and at 7.5 to 8 years of age, but not at 9 months post term (see Fig. 1). Of the 834 surviving subjects, 799 were still resident in the United Kingdom. Altogether 782 (98%) were assessed at 7.5 to 8 years of age using the Wechsler intelligence scale for children (revised Anglicized version: WISC-R UK). To keep testing time to a reasonable length given that we also measured various
STUDY 1.  
Comparing banked donor milk with preterm formula.

Mother was asked whether she wished to provide her own expressed breast milk for her baby

\[ \downarrow \]
No

\[ \downarrow \]
Randomise to:
Banked donor milk vs. Preterm formula
\textit{as sole diets}  
\( n = 159 \)

\[ \downarrow \]
Yes

\[ \downarrow \]
Randomise to:
Banked donor milk vs. Preterm formula
\textit{as supplements to mother's milk}  
\( n = 343 \)

Follow up:  
9 months post term
18 months post term
7.5 to 8 years

STUDY 2.  
Comparing term with preterm formula.

Mother was asked whether she wished to provide her own expressed breast milk for her baby

\[ \downarrow \]
No

\[ \downarrow \]
Randomise to:
Term formula vs. Preterm formula
\textit{as sole diets}  
\( n = 160 \)

\[ \downarrow \]
Yes

\[ \downarrow \]
Randomise to:
Term formula vs. Preterm formula
\textit{as supplements to mother's milk}  
\( n = 264 \)

Follow up:  
18 months post term
7.5 to 8 years

FIG. 1. The study design.

Anthropometric and health outcomes, we used an abbreviated version of the WISC-R with five subtests: similarities, arithmetic, and vocabulary (verbal scale), block design and object assembly (performance scale). Overall WISC-R intelligence quotient (IQ) assessed from these five subscales has a correlation coefficient with the full WISC-R IQ of over 0.96 (17). We also measured word reading and arithmetic performance using the word-reading and basic number skills subscales of the British Ability Scales.

Many test items are more difficult for children with impaired manipulative skills; those with hearing impairment will have some difficulty with verbal tasks and understanding instructions, and blind children are unable to undertake most of the tasks. In these cases, test performance will be an unreliable measure of cognitive status. We therefore excluded data from children who had evidence of neuromotor or neurosensory impairment from most of the analyses reported here. We also excluded children who had insufficient data in the neonatal period to calculate steady-state weight gain reliably.
EARLY GROWTH AND LATER DEVELOPMENT

### TABLE 1. Characteristics of infants in four categories of neonatal weight gain

<table>
<thead>
<tr>
<th>Categories of neonatal weight gain (g/kg·d)</th>
<th>&lt;12.32</th>
<th>12.32 to &lt; 14.68</th>
<th>14.68 to &lt; 17.12</th>
<th>17.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestation (SD) in weeks</td>
<td>31.4 (2.8)</td>
<td>31.4 (2.8)</td>
<td>31.1 (2.7)</td>
<td>31.5 (2.7)</td>
</tr>
<tr>
<td>Mean birthweight (SD) in grams</td>
<td>1426 (293)</td>
<td>1406 (306)</td>
<td>1381 (297)</td>
<td>1416 (293)</td>
</tr>
<tr>
<td>Mean (SD) birthweight ratio (a)</td>
<td>0.83 (0.18)</td>
<td>0.82 (0.18)</td>
<td>0.83 (0.20)</td>
<td>0.82 (0.20)</td>
</tr>
<tr>
<td>% male</td>
<td>48%</td>
<td>43%</td>
<td>49%</td>
<td>53%</td>
</tr>
<tr>
<td>Median (25th, 75th percentiles) days on &gt; 30% oxygen</td>
<td>5 (1, 11)</td>
<td>3 (0, 9)</td>
<td>2 (0, 8)</td>
<td>2 (0, 6) (b)</td>
</tr>
<tr>
<td>Median (25th, 75th percentiles) total IV fluids in ml</td>
<td>783 (267, 2314)</td>
<td>900 (382, 1538)</td>
<td>482 (130, 1141)</td>
<td>474 (199, 810)</td>
</tr>
<tr>
<td>% on preterm formula (vs. donor milk or standard term formula)</td>
<td>34%</td>
<td>38%</td>
<td>53%</td>
<td>79% (d)</td>
</tr>
</tbody>
</table>

\(a\) Birthweight ratio is a measure of size for gestation, calculated as birthweight/mean birthweight for sex and gestation.

\(b\) \(p < 0.01\) by Kruskal-Wallis one-way ANOVA.

\(c\) \(p < 0.0003\) by Kruskal-Wallis one-way ANOVA.

\(d\) \(p < 0.00001\) by \(\chi^2\) analysis.

FACTORS ASSOCIATED WITH WEIGHT GAIN IN THE NEONATAL PERIOD

Altogether, 598 surviving children fulfilled the criteria for inclusion in these analyses and were assessed at 7.5 to 8 years. Of these, 300 were in study 1 and 298 in study 2. In Table 1, neonatal weight gain is categorized into four equal groups. Children with the lowest weight gain were less likely to have been fed preterm formula, had more intravenous fluids, and had more prolonged respiratory illness. Data are shown for days in more than 30% oxygen, but similar associations were seen with days of mechanical ventilation.

In a regression model, those factors significantly associated independently with weight gain in the neonatal period were sex of the infant (higher weight gain in boys), whether the infant was fed preterm formula, days in more than 30% oxygen, and birthweight. Preterm formula feeding improved weight gain, whereas weight gain fell with increasing days in more than 30% oxygen and with higher birthweight.

In separate analyses including only data from children whose mothers chose to provide breast milk, neonatal weight gain fell as the proportion of intake provided by maternal milk increased. From the regression coefficient, there was a 0.1 g/kg·d decrease in weight gain as the proportion of intake as mother’s milk increased by 10%.

NEONATAL WEIGHT GAIN AND LATER WEIGHT

Neonatal weight gain was positively associated with weight at 9 months post term, both before and after adjusting for factors associated with neonatal weight gain in a regression model \((p = 0.009\) after adjustment).
FACTORS ASSOCIATED WITH PERFORMANCE SCORES AT 7.5 TO 8 YEARS

We have shown previously that many social and demographic factors are related to cognitive performance (18). All the scores were higher in children whose mothers had chosen to provide breast milk (16,18) or who were of higher social class or better educational attainment, and they were lower as a function of increasing birth order. Performance IQ was 3 points higher in boys \((p = 0.008)\), and both reading and arithmetic scores were significantly higher in girls \((p < 0.001\) and \(< 0.03\), respectively).

In separate univariate analyses, the performance measures at 7.5 to 8 years were significantly associated with some of the factors influencing neonatal weight gain. Overall, verbal, and performance IQ increased with birthweight \((p = 0.008, 0.02,\) and \(0.007,\) respectively) and decreased with the number of days in more than 30% oxygen \((p < 0.001\) in all cases). Both reading and arithmetic scores were significantly lower with increasing number of days in more than 30% oxygen \((p < 0.01\) and \(< 0.001,\) respectively).

NEONATAL WEIGHT GAIN AND PERFORMANCE SCORES AT 7.5 TO 8 YEARS

There was no significant influence of neonatal weight gain on whether the child had neuromotor impairment (Table 2). Among unimpaired children, overall and verbal

<table>
<thead>
<tr>
<th>Categories of neonatal weight gain (g/kg·d)</th>
<th>&lt;12.32</th>
<th>12.32 to &lt; 14.68</th>
<th>14.68 to &lt; 17.12</th>
<th>17.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with neuromotor impairment</td>
<td>7.5%</td>
<td>6.5%</td>
<td>5.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Mean overall IQ (SD) at 7.5 to 8 years</td>
<td>96.5 (16.3)</td>
<td>99.7 (15.6)</td>
<td>101.3 (15.3)</td>
<td>101.7 (12.7)(^a)</td>
</tr>
<tr>
<td>Mean verbal IQ (SD) 7.5 to 8 years</td>
<td>94.1 (18.1)</td>
<td>99.4 (17.8)</td>
<td>100.3 (18.5)</td>
<td>100.5 (14.8)(^b)</td>
</tr>
<tr>
<td>Mean performance IQ (SD) at 7.5 to 8 years</td>
<td>103.0 (17.2)</td>
<td>103.3 (16.6)</td>
<td>104.7 (14.3)</td>
<td>107.0 (13.1)</td>
</tr>
<tr>
<td>Mean reading score (SD) 7.5 to 8 years</td>
<td>45.8 (11.1)</td>
<td>48.6 (12.3)</td>
<td>48.7 (13.2)</td>
<td>46.3 (11.8)</td>
</tr>
<tr>
<td>Mean arithmetic score (SD) at 7.5 to 8 years</td>
<td>44.4 (11.0)</td>
<td>45.8 (10.1)</td>
<td>46.8 (12.3)</td>
<td>46.1 (8.7)</td>
</tr>
</tbody>
</table>

\(^a\) \(p 0.01\) by ANOVA.  
\(^b\) \(p 0.003\) by ANOVA.
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TABLE 3. Outcome measures at 7.5 to 8 years: are they significantly positively related to neonatal weight gain? (Findings from regression models)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>All subjects</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall IQ</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reading score</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arithmetic score</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>All subjects</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall IQ ≥ 85</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Verbal IQ ≥ 85</td>
<td>✓</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Performance IQ ≥ 85</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reading score ≥ 38</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arithmetic score ≥ 38</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

✓ Denotes a significant association.

IQ at 7.5 to 8 years rose significantly with increasing neonatal weight gain. There was no significant influence of neonatal weight gain on reading or arithmetic scores from the British Ability Scales.

As described earlier, there is a considerable degree of interrelationship between neonatal, social, and demographic measures with respect to their influence on later performance. To test whether weight gain in the neonatal period independently influences IQ, reading, and arithmetic scores we therefore used regression models, adjusting for other potentially influential factors. Independent factors in the initial models were birthweight, gestation, days in more than 30% oxygen, volume of intravenous fluids in the neonatal period, whether the infant was fed preterm formula (as sole diet or supplement), whether the mother chose to provide her breast milk, sex of the infant, social class, mother’s educational attainments, and birth order of the child. Factors not independently related to the outcome measure ($p < 0.2$) were removed from the final models. All analyses were performed using data from both sexes, then in boys and girls separately.

In addition to investigating performance scores as continuous variables in linear regression models, we considered it important to look for predictors of good versus “suboptimal” outcome, the latter defined in this study as IQ scores below 85 and scores on the reading and arithmetic scales below 38. “Suboptimal” scores were more than 1 SD below the population mean of the test standardization sample, a definition that has been used by some educationalists for mild educational impairment. Analyses on these categorized variables (“good” versus “suboptimal” performance) were undertaken using logistic regression models.

The results of these regression analyses (excluding data from children with neuro-motor or neurosensory impairment) are summarized in Table 3. The only significant finding was that there was an association between better neonatal weight gain and verbal IQ scores of 85 or higher. This was, however, largely seen in boys, not girls. In boys, the odds of a score of 85 or more were increased by 0.9 for each 1 g/kg·d increase in neonatal weight gain.
We considered the possibility that the association between neonatal weight gain and later performance in males was because of causal associations between receiving preterm formula and both better neonatal growth and better developmental outcome. Since weight gain and randomized diet are closely related, inclusion of both factors in the model is not an ideal way to decide which is the major causal factor. However, we found that after inclusion of neonatal weight gain in the model there was no significant advantage from being fed preterm formula.

In separate regression models including all subjects, there was no association between neonatal weight gain and neuromotor impairment.

POSTNEONATAL GROWTH AND LATER COGNITIVE PERFORMANCE

Regression models similar to those given earlier were constructed to include both neonatal weight gain and weight at 9 months post term, with performance scores as dependent variables. Results are summarized in Table 4. It should be noted that because only children in study 1 were seen at 9 months, these analyses are restricted to unimpaired children in that study and did not involve the whole unimpaired population as in Table 3. In the combined group of boys and girls, overall, verbal, and performance IQ increased with weight at 9 months post term. Regression coefficients and $p$ values are shown in Table 4. In boys there was a significant positive association between weight at 9 months and overall, verbal, and performance IQ scores, as well as reading score. No influence was seen in girls. Boys were also significantly more likely to have overall or verbal IQ and reading and arithmetic scores over 85 as weight at 9 months increased (Table 4).

In further analyses we investigated whether being fatter at 9 months conferred a later cognitive advantage. Body mass index was calculated as weight/length$^2$ (kg/m$^2$). In univariate analyses there was a significant increase in all the measures, apart from

<table>
<thead>
<tr>
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<th>All subjects</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall IQ</td>
<td>+2.3 (0.02)</td>
<td>+3.2 (0.001)</td>
<td>—</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>+2.4 (0.002)</td>
<td>+3.4 (0.003)</td>
<td>—</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>+2.3 (0.005)</td>
<td>+2.8 (0.01)</td>
<td>—</td>
</tr>
<tr>
<td>Reading score</td>
<td>—</td>
<td>+2.3 (0.01)</td>
<td>—</td>
</tr>
<tr>
<td>Arithmetic score</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Overall IQ $\geq$ 85</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Verbal IQ $\geq$ 85</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Performance IQ $\geq$ 85</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reading score $\geq$ 85</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Arithmetic score $\geq$ 85</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$ Values shown (in upper portion of table) are regression coefficient ($p$ value). The regression coefficient indicates the influence of 1 kg increase in weight at 9 months on each outcome measure.

$^b$ ✓ Denotes a significant association.

Data are from study 1 only.
TABLE 5. Outcome measures at 7.5 to 8 years: are they significantly positively related to body mass index (weight/height\(^2\)) at 9 months postterm? (Findings from regression models.)

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall IQ</td>
<td>+1.6 (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>+1.2 (0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading score</td>
<td>+1.1 (0.009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic score</td>
<td></td>
<td></td>
<td>+1.6 (0.02)</td>
</tr>
</tbody>
</table>

Overall IQ ≥ 85
Verbal IQ ≥ 85
Performance IQ ≥ 85
Reading score ≥ 85
Arithmetic score ≥ 85

\(a\) Values shown (in upper portion of table) are regression coefficient (p value). The regression coefficient indicates the influence of 1 unit increase in body mass index at 9 months on each outcome measure.

\(b\) Denotes a significant association.

Data are from study 1 only.

the word-reading score, with increasing body mass index. For example, overall IQ was 96.5 (SD 14.6) in the lowest quarter for body mass index at 9 months, rising linearly to 102.4 (SD 14.5) in the highest quarter (\(p = 0.035\) by analysis of variance).

In linear regression models where we applied the adjustments described earlier and included neonatal weight gain, increasing body mass index was associated with significantly higher overall and verbal IQ scores and higher reading scores in boys and girls combined (Table 5). In logistic models a higher body mass index was associated with significantly reduced odds of a reading score below 38 in males and females separately as well as combined, and reduced odds of a low arithmetic score in both sexes combined.

We also considered the possibility that head circumference gain in the neonatal period or head circumference at 9 months may be more influential than weight gain or weight in respect of later performance. This proved not to be the case. The associations were complex. Neonatal head circumference gain was negatively associated with later performance: the greater the head circumference gain, the lower were the later scores. With neonatal head circumference gain and weight and head circumference at 9 months in the regression models, weight at 9 months was still the predominant influence. When head circumference at 9 months replaced weight at 9 months in models (see Table 4), head circumference was not significantly related to any of the outcomes investigated.

COMMENT

That the influence on later performance of both neonatal weight gain and weight at 9 months is confined to males is consistent with our findings on the effect of early nutrition on later cognitive performance. At each follow-up point we have found that
the advantage from being fed preterm formula (versus donor breast milk or term formula) is greater in boys than in girls (9–12). Animal studies have also suggested that males are more vulnerable to poor early nutrition than females. Smart (19) reviewed 165 animal studies investigating the influence of malnutrition on learning and showed that the number of studies in which undernourished animals had poorer learning than controls \((n = 80)\) greatly outweighed the number of those favoring the controls \((n = 12)\), but the advantage was seen predominantly in males. Also, in a study by Fitzhardinge and Steven on small-for-gestational-age full-term infants (20), only males had later cognitive deficits.

There are other possible explanations for our findings relating to weight at 9 months post term. Repeated illness and hospital admissions during that period could have influenced both growth and the ability to elicit, respond to, and learn from interactions with adults and siblings. We therefore reanalyzed these data, including the number of hospital admissions in the first 9 months post term. There was a significant independent negative association between the number of hospital admissions in the first 9 months post term and both overall and verbal IQ. With number of hospital admissions in the model, the magnitude of the effect of weight at 9 months post term on later IQ was slightly diminished but remained statistically significant in every case. For example, among boys and girls combined, inclusion of number of hospital admissions up to 9 months post term in the model reduced the regression coefficient for the influence of 9 months weight on overall IQ from 2.3 to 2.1 \((p = 0.02\) and 0.002, respectively). For every hospital admission, overall IQ at 7.5 to 9 years was reduced by 1.5 \((p = 0.02)\).

Our finding that there was a small significant increase in overall and verbal IQ scores with increasing body mass index is important for clinical management. It suggests that if increasing nutrient intake in the postneonatal period results in babies becoming fatter, rather than having proportionate weight and length gain, this may still be advantageous in terms of later performance. On the grounds of adult health there is also evidence of benefit in males with increasing weight at a year. Standardized mortality ratios for death from ischemic heart disease fell from 111 in men who weighed 8.2 kg or less at 1 year to 42 in those who weighed 12.3 kg or more (21).

There were too few subjects with extremely low birthweight to permit separate analyses in that group. In analyses restricted to subjects weighing under 1,500 g we failed to replicate the preceding significant findings. However, results were very similar when we confined analyses to subjects who were in more than 30% oxygen for more than 24 hours (62% of the population).

**SUMMARY**

Our data suggest that weight gain both in the neonatal period and in the first year of life are important for the future cognitive performance of children born with low birthweight. Weight at 9 months post term was more influential for later cognition than neonatal weight gain, and the influence in both cases was seen predominantly in males. Increase in body mass index was also associated with a small increase in later perfor-
mance scores. Our data raise the hypothesis that in boys the postneonatal period is a more critical period for brain growth and maturation than the neonatal period. In girls we were able to detect little evidence that early growth influenced later performance.

Optimizing postnatal growth of male children born preterm should be a priority. The results from randomized trials of nutrient-enriched postdischarge formula in such children should help resolve some of the issues raised here.

REFERENCES


DISCUSSION

Prof. Haschke: Were the infants who were not included in the analysis treated as dropouts or as noncompliant? These represented 25% of the cohort.
Dr. Morley: These were children mostly who had some sort of motor or neurosensory problem. I made the decision not to include them in the analysis because I thought they would cloud the issue. You could argue that it was wrong to omit these children. However, these IQ tests rely on children making patterns with blocks and assembling puzzles. A child with neuromotor impairment can't do that properly, so you are not actually measuring their cognitive performance. And if they can't hear properly, this will have delayed the development of language and may impair their ability to understand instructions. I felt that if we were going to look at these questions properly, we needed a cohort with the minimum of unnecessary confounding factors.

Dr. Rigo: You had two different cohorts of infants receiving only preterm formula, one in Cambridge and one in Norwich and Sheffield. When you looked at neurodevelopmental scores at 7 years, was there a significant difference between those two cohorts? I think that you published a Bayley score at 18 months in the two groups, and if I remember correctly there was a difference between the infants who were fed preterm formula in Cambridge and those fed preterm formula in Norwich and Sheffield. It is therefore very important to know whether the two cohorts of preterm infants fed preterm formula have persisting differences in their Bayley scores and neurodevelopmental outcome.

Dr. Morley: The difference in the scores between the two preterm formula groups is accounted for by social and demographic differences between the two populations. Social class in the UK has a powerful influence. It accounts for more variance in IQ than in most other countries.

Prof. Mow: Can you tell us what kind of feeding these babies received after discharge from the neonatal department?

Dr. Morley: We had no control over that whatsoever. After they left the hospital, they were fed as their parents and their medical advisors chose. So we only knew really what happened to them in the neonatal period.

Prof. Moro: Did you find any correlation between gain in length and IQ?

Dr. Morley: There was no association. To my surprise, weight was really the most powerful influence. It was more powerful than head circumference. Head circumference gain in the neonatal period was negatively associated with later performance—the faster the baby’s head grew in the neonatal period, the lower the later scores. Weight and head circumference at 9 months were quite closely correlated. When you have two very closely correlated factors in a model, strange things may happen. But it looked as though weight was in fact the most important influence.

Prof. Ziegler: I am tremendously interested in this type of analysis. What your remarkable study has shown is that something related to nutrition in early infancy in premature infants matters as far as long-term outcome is concerned, but we still don't know what this is. If it is protein—or maybe energy—that differs, then this should show up in the weight gain during the period of hospital inpatient management. You did the analysis, and I was delighted to see that you showed a relation between later IQ and weight gain in the nursery, but then you explained it away! Unfortunately, you presented too much information on your slides for it to be possible to identify the important confounders in your equation; maybe some are unimportant. The message I take away is that there is a relation between weight gain in the nursery and later IQ, which confirms for me that it is perhaps protein or energy that has made the difference.
Dr. Morley: The problem is that the children who gained weight less well were those who were most sick, and being sick does no good for the brain. For example, there was an inverse relation between later IQ and the number of days in more than 30% oxygen. We had to adjust for such factors, and when this was done the effect of weight gain was almost lost. The issue now is whether, if we give these infants more nutrients, we can get them to grow better, and whether that will improve their outcome in the long term. Maybe Dr. Lucas would like to comment?

Prof. Lucas: You need to give me another few weeks. We have just started to clean the data on a large randomized postdischarge trial. Our very preliminary findings suggest that growth is promoted beyond the period of dietary randomization. So this is going to be quite exciting, but it’s too early to announce the results.

Dr. Chessex: You showed that the infants who gained weight more rapidly had received less total parenteral nutrition (TPN) by volume. I suggest a hypothesis: Maybe the volume of TPN received is important, because by infusing TPN you’re infusing high doses of peroxides. Girls are better protected against peroxides, and this could explain why they appear to have a better outcome. Have you looked at that variable more closely?

Dr. Morley: TPN was not one of the factors that came out as significant in the models when I was looking at performance. We could argue about the way I did those models. What I did was to enter all the factors that I thought were of interest and then remove from the final model any where the association was less than $p = 0.02$. I plan to repeat all these analyses on the basis of how much each variable affects the regression coefficient, which is going to be extremely time-consuming. All I can say at present is that in the model chosen the volume of intravenous feeds was nowhere near being a significant factor.

Prof. Heird: I was intrigued by your association between body mass index (BMI) and neurodevelopmental scores. But I’m also impressed by the fact that most babies who grow reasonably normally on any kind of regimen probably have a high BMI, in other words they’re short and fat. To what extent do you think the effect you showed really reflects the BMI? Maybe it is a reflection of the fact that the babies who aren’t short and fat are the ones who had other problems along with an inadequate intake. The association may not necessarily be with BMI, but with some other factor.

Dr. Morley: I agree. More work needs to be done on this. The problem is that weight and BMI are obviously highly interrelated. Models become extremely unstable when they include a number of closely related factors.

Prof. Dimita: From a biological point of view, I cannot understand how body growth influences cognitive development positively whereas brain growth—that is, head circumference—has a negative effect on IQ. We have a great deal of epidemiological data showing that prenatal and postnatal growth of the head—that is, the brain—has a positive influence on IQ.

Prof. Lucas: Maybe I could answer that. I suggest that head circumference growth may not be as informative as other variables such as weight in preterm infants. Large head circumference gains may reflect ventricular dilatation in premature babies and therefore may be pathological rather than indicate brain growth. The other important thing is that the sickest and smallest babies have the greatest degree of skull deformation (side-to-side flattening), because they have poorly mineralized bones. Obviously, the flatter the skull is from side to side, the larger the head circumference in relation to brain volume. So the sickest babies will have spuriously large heads and
will be the ones who are likely to have the worst outcome. So the effects of brain growth on neurodevelopment may be canceled out by factors that affect the apparent size of the head when you put a tape round it.

**Dr. Walker:** Did you use the complete WISC in some children to see if the results with the modified WISC were substantiated? And in the individuals whom you left out of the study because they had defects such as hearing loss and so on, did you do an assessment using tests for measuring IQ in handicapped people to see whether or not there was a correlation between weight gain and outcome in that group of patients?

**Dr. Morley:** We did not do the full WISC on any of the children, mainly because we were measuring a lot of other things, so there simply wasn’t time. We did extensive anthropometry and a fair amount of motor testing, which we still haven’t reported, and we also examined various cardiovascular outcomes. By the time of follow-up, the children were spread around the country, and from a logistic point of view we needed to keep the testing within 1.5 hours. So we could not do the full-scale IQ, which was a pity. I did not include here IQ data from children with neuromotor or neurosensory impairment.

**Prof. Lucas:** I’d like to address that a little further. Clearly, having demonstrated major differences between groups on the abbreviated form of the WISC in at least one trial, it is mandatory that we undertake much more sophisticated neurodevelopmental testing. Now that the children have reached 14 years, we can test them over a half day or even a whole day, and we can do very sophisticated neurodevelopmental testing and brain studies. If there really are quite subtle effects of diet on lifetime cognitive or motor performance, we ought to be able to identify them.

**Prof. Cooper:** Have you looked at the head circumference growth in the neonatal period and at 9 months in the group that you excluded because of sensorimotor handicap?

**Dr. Morley:** No, I haven’t done any detailed analysis on that group at all, though the data are available and could certainly be analyzed.

**Dr. Schanler:** Do you have any information on differences in growth in the neonatal period and after discharge from hospital in infants who were fed their own mother’s milk versus those who received banked milk or formula?

**Dr. Morley:** Not many of these babies actually went home breastfed, even among the ones whose mothers expressed breast milk in the neonatal period, so that was not a major issue in these cohorts. In terms of the randomized comparison between banked donor breast milk and preterm formula, there was a highly significant influence. The children who were fed banked donor breast milk grew significantly less well in terms of weight gain, length gain, and head circumference gain than those fed on the preterm formula. In the groups where the randomized diets were fed as a supplement to mother’s milk, as the proportion of mother’s milk in the diet increased so neonatal weight gain decreased. Thus the more mother’s milk the baby got, the less was its neonatal weight gain. Of course this raises the question of the quality of the nutrition. There may be other issues at stake, apart from just growing rapidly.

**Prof. Ziegler:** You showed a strong association between weight at 9 months and IQ at 8 years. I wonder what that means. We know that premature babies very commonly fail to grow in the first 2 to 3 years. That in itself is a bit of a mystery. But I wonder whether weight at 9 months is simply a marker of IQ at 8 years, rather than the other way round, which is what I think you implied. In other words, if you’re small, that predestines you to have a low IQ at 8 years. What are your thoughts on this?
Dr. Morley: These are basically exploratory analyses and I don't think that I would suggest that they give us any clues as to causality. All I'm telling you is that there is an association between these various measures of performances at 7.5 to 8 years and weight at 9 months post term. What the reason for that is I don't know. It is still possible that there is some confounding that I haven't adjusted for—for example, hospital admissions. Unfortunately, although we know the numbers of admissions, we don't know the lengths of stay.

Prof. Fazzolari: Have you any explanation for the differences in performance scores between males and females at 9 months?

Dr. Morley: What we have shown throughout our study is that if children were fed a suboptimal diet, or if their growth was poor, it was the boys whose performance was most affected. It was not that there was a great overall difference between boys and girls, but that the boys seemed to be more vulnerable to the adverse influences of suboptimal nutrition or poor growth. I don't know the reason for that.

Prof. Fazzolari: Was the preterm formula that you used supplemented with LC-PUFA and nucleotides?

Dr. Morley: No, these were formulas in the early 1980s.