In this paper we review the evidence for such early nutritional influences on cognitive function.

There has been a long standing interest in whether undernutrition, at a sensitive or critical period of brain growth or maturation could have a long lasting or permanent 'programming' influence on later cognitive performance. One noteworthy example of a nutritional influence on cognitive function is maternal iodine deficiency, which may result in frank cretinism or reduced cognitive function and school performance in the offspring. These nutritional effects, mediated here by an endocrine mechanism, are irreversible. A key question is whether other general or specific nutritional insufficiencies can likewise influence or 'programme' cognitive function. Given the extent and range of nutritional deficiencies worldwide, this question is of great significance for mankind.

Animal studies have demonstrated that nutritional deprivation affects measures of performance, but it is difficult to extrapolate from such measures in animals (largely rodents) to human cognition, though they are of importance in establishing both the principle and mechanism of any associations.

Causal links between early nutrition and later cognitive performance in man have been difficult to establish. Nutritional deprivation studies would clearly be unethical, so that most investigations have been of nutritional supplementation in populations suffering poverty and undernutrition, which may confound the relationship, making the influence of undernutrition itself difficult to assess. The greatest need, identified by Birch in 1968, is for randomised trials of nutritional intervention and outcome in man. Some such studies have been undertaken relatively recently.

As well as overall or protein-energy nutrition, there is considerable interest in whether a deficiency of specific nutrients at a sensitive or critical period for brain development could result in a long term or permanent cognitive deficit. The role of dietary iron intake in later cognitive function has been extensively researched in both animals and humans. Zinc deficiency has also received attention in this respect. That breast fed infants perform better than those fed artificially, even after adjusting for potential confounding factors, has led to the hypothesis...
that dietary long chain polyunsaturated fatty acids, most notably docosahexaenoic acid (DHA, found in human milk but not in conventional formulas) are critical nutrients for neurodevelopment.

Animal studies

Two key areas that have received attention in animal experiments are the impact of protein-energy undernutrition and iron deficiency on later learning and behaviour.

Protein-energy undernutrition

Does undernutrition influence later behaviour? Rodents have been widely used as experimental models for determining whether there is an association between early nutritional deprivation and performance because their brain growth spurt occurs during the suckling period, when nutrition can readily be modified, for example by nutritional deprivation of the mother or an increase in litter size. The results of these studies, many of which demonstrated behavioural disadvantages for underfed pups, were open to alternative explanations. Changes in litter size or maternal nutrition, plus any effect of poor nutritional status on the pup's interest in social interactions, inevitably affected the interaction between pup and mother, which is important for behaviour. However, when artificially reared underfed and well fed rat pups, and mother-reared underfed and well fed pups were compared, the underfed animals performed less well on behavioural measures, whether or not they were reared by their mother. Interestingly the disadvantage for the underfed rats was greater if they were artificially fed, raising the possibility that either maternal stimulation or one or more factors in fresh maternal milk partly ameliorated the effect of poor nutrition on brain growth or development.

A review of studies comparing the performance of well nourished versus previously undernourished rats, showed that a disadvantage for undernourished animals was significantly more likely if the period of undernutrition included gestation. Interestingly, the advantage was most often seen in male animals.

What are the underlying mechanisms of these nutritional effects? The rat brain is less mature at birth than the human brain and postnatal undernutrition in rats (at a stage of rapid brain growth comparable with
the third trimester of human pregnancy) has been shown to result in impairments in a number of different aspects of brain growth and function\textsuperscript{6}. For example, the effect of undernutrition on the developing cerebellum was shown to result in a 15\% deficit in DNA (a proxy for cell number). Although cortical neuronal cell numbers were not reduced by malnutrition, other cortical structures were affected. For example, glial cell numbers were significantly reduced, as was the complexity of cortical dendritic branching and the length and width of synaptic reactive zones. Evidence emerged that some of these changes were reversible and cortical glial cell number and synapse to neurone ratio can improve with good postnatal nutrition. Other structural changes, like reduction in the number of hippocampal granule cells, have proved irreversible\textsuperscript{7}, though previously malnourished and rehabilitated animals had an increase in the number of synapses per hippocampal neurone\textsuperscript{8}. These findings illustrate the difficulty of predicting the impact of malnutrition on cognitive function from observed neuroanatomical changes.

Early malnutrition also produces long term alterations in neurotransmitter metabolism, one being down-regulation of β-adrenergic receptors, with possible effects on ability to respond to stressful situations.

Some areas of behaviour in rats were affected whereas others were not, and the extent of recovery after re-feeding varied between tasks. For example, in one study there was no effect of undernutrition on position discrimination, a reversible effect on brightness discrimination but a permanent impairment of pattern discrimination.

Several studies demonstrated that stimulation (like stroking rat pups) during or soon after the period of undernutrition ameliorated later behavioural deficits, giving rise to the hypothesis that early undernutrition resulted in a long-lasting impairment in exploratory or leaning behaviour, which can be ameliorated by stimulation.

Whether such changes in brain structure or function, or in behaviour can be extrapolated to the human and whether they would cause long term cognitive impairment are open to debate.

**Iron deficiency**

Iron is an essential part of a number of haem-containing mitochondrial enzymes, like flavoproteins. It is also important as a co-factor for enzymes involved in the metabolism of catecholamines, including dopamine, the major neurotransmitter in the extra-pyramidal system.

Studies in the rat have shown that early iron deprivation (at 10 days) led to a permanent reduction in brain iron and dopamine D\textsubscript{2} receptor site
concentration despite subsequent iron sufficiency, though at later ages the deficits were reversible with iron supplementation⁹. Rats with the permanent deficits performed significantly less well than controls in maze learning tasks.

Whether there is a similar critical period when iron deficiency permanently affects the human brain is explored in this article.

**Studies of nutrition and neurodevelopment in humans**

**Evidence from epidemiological studies**

*Protein-energy undernutrition:* Numerous observational studies explore whether children with severe or mild to moderate undernutrition or those whose growth was stunted (low weight for height) perform less well than adequately nourished and normally grown childrenⁱ⁰,¹¹. In many, though not all, studies, poor nutritional status has been associated with lower cognitive or attainment scores. However, retrospective studies of subjects who were malnourished versus well nourished in childhood are generally too confounded to yield interpretable data, since undernourished children came largely from poor and undernourished populations, with higher childhood morbidity and parents who were less able to care for and stimulate their children. Attempts have been made to match controls for social background, with similar findings.

In Guatemala a large study was conducted in four villages, with similar populations and lifestyle. In two a high energy, high protein drink was supplied and in the others a low calorie one; both were available *ad libitum* to pregnant women and children up to the age of 7 years. Beneficial effects of supplementation with the high energy, high protein drink were seen at the end of the intervention period and in measures of school achievement in adolescence¹²,¹³. Sibling controls have also been used. In about half of these studies the index undernourished children performed less well than the control siblings, though the siblings will probably have been exposed to some degree of undernutrition¹¹.

*Breast milk:* Children who were breast fed have often been shown to perform better in terms of tests of development or cognition, verbal ability or school performance¹⁴−¹⁸. Results have been similar in both children born at term and preterm. However, there are two major sources of confounding.
1. The intimacy of breast feeding may be important for infant development.

2. Mothers who choose to breast feed are different from mothers who choose not to. In studies conducted on subjects born in the last few decades, the findings are confounded by the fact that breast fed children come from a higher socio-economic group than those fed formula. Thus any differences may reflect higher parental educational level, better nutrition and housing, a more stimulating environment, better access to pre-school education or a more positive attitude to education.

Many studies have adjusted for a range of potentially confounding factors and in most cases the advantage for breast fed children has remained. There is a need, however, to devise studies which avoid confounding. In two parallel trials of neonatal nutrition in children born preterm (described in detail below, Fig. 1), we found that even after adjusting for confounding factors there was a developmental advantage in both Bayley Mental Development Index at 18 months post term and in IQ at 7.5–8 years for those children whose mothers had chosen to provide their own breast milk. In this study the mothers expressed their breast milk and it was fed to the infant via a nasogastric tube. When we considered only those infants whose mothers did not go on to breast feed, the advantage was unchanged, demonstrating that the observed developmental advantage for preterm children receiving breast milk is independent of any closeness or intimacy associated with breast feeding itself.

Two studies were conducted on subjects born at a time when artificially fed children came from the most socio-economically advantaged stratum of society. Hoeffer studied children born in the US between 1915–1921 and showed that breast fed children performed better than those who were artificially fed, though children who were exclusively breast fed beyond 9 months did less well. A study of elderly subjects born in the UK in the 1930s showed that despite lower socio-economic status those who were breast fed had higher unadjusted IQ.

Iron deficiency: Children who have iron deficiency anaemia (in some cases after being randomised to receive iron supplementation) have been shown to have lower developmental scores than those with haemoglobin levels in the accepted normal range. Infants who were studied by Lozoff et al in Costa Rica were followed up at the age of 5 years. Children who had been anaemic in infancy (haemoglobin <10 g/100 ml) had lower developmental scores at age 5 than those who had not been anaemic, regardless of treatment group and despite similar mean current haemoglobin values in the two groups. These results were confounded...
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**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

- No
- Randomise to Banked donor milk vs Preterm formula as sole diets
  - n=159

- Yes
- Randomise to Banked donor milk vs Preterm formula as supplements to mother's milk
  - n=343

**STUDY 2**, comparing term with preterm formula

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

- No
- Randomise to Term formula vs Preterm formula as sole diets
  - n=160

- Yes
- Randomise to Term formula vs Preterm formula as supplements to mother's milk
  - n=264

Fig. 1 Study design.

by socio-economic differences between previously anaemic and non-anaemic children but, even after adjustment for these, the anaemic group performed less well. Whether this was because important confounding factors were unidentified or inadequately measured is debated. However, these data raise the possibility that iron deficiency anaemia in infancy does have a longer term negative influence on cognition.

**Evidence from randomised trials**

*Protein-energy undernutrition:* Randomised trials of nutritional interventions have been undertaken largely in developing countries in high risk families or children suffering mild to moderate undernutrition or stunted growth (low height for age).

In a study in Taiwan nutrient supplementation was given to high risk mothers during pregnancy and lactation without giving supplements to their offspring. Mothers (n=255) were randomly allocated a nutrient supplemented or placebo drink. Children of supplemented mothers had a small but significant advantage in motor development at 8 months, but
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mental scores were unaffected and there were no IQ differences at 5 years of age.

In Bogota, Colombia, 433 nutritionally at risk pregnant women were randomly allocated to 6 groups. They or their children (or both) received supplementation during different periods up to 3 years. In two groups the offspring also received stimulation. The intervention period lasted until children reached 3 years. At the age of about 7 years nutrient supplemented children performed better in Reading Readiness tests\(^{26,27}\).

There have been a number of intervention studies in children, though many were small. In Jamaica\(^{28}\), 129 stunted children aged 9–24 months were randomly allocated to four groups; non-intervened, nutrient supplemented, supplemented and stimulated, or stimulated alone. After a two year intervention both supplemented and stimulated children had significantly higher Griffiths mental development scores than the control group. Children who were both supplemented and stimulated had the highest scores.

In a homogeneous population living on tea plantations in West Java, day-care centres were randomly designated nutrient supplement providing centres or control centres, for 6–20 month old infants. The nutritional intervention lasted 90 days, after which supplemented children had significantly higher Bayley motor scale scores\(^{29}\).

Longer term post-intervention data are not available from these studies.

In 1982 we started a nutritional intervention study in low birthweight children, a group who are at high risk of poor early nutrition and failure to thrive and are at a stage of rapid brain growth and maturation. Milks routinely fed to them at that time differed substantially in nutrient content, ranging from donor breast milk (from unrelated breast feeding mothers in the community) to a standard term or nutrient enriched preterm formula designed to meet the special nutrient needs of babies born preterm, a time of rapid growth. It was both a practical and ethically undertaken randomised trial; the results were needed for informed management decisions. Furthermore, there were large differences in nutrient content between the allocated milks, so we could investigate, in a randomised prospective intervention trial, whether early nutrition influences later cognitive status. Altogether 926 infants, born weighing under 1850 g in 5 centres in the UK in 1982–1984 were randomly allocated their early enteral diet. The randomisation was as shown in Figure 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 sole diet and supplement groups were separately randomised.
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and data could, therefore, be analysed separately for these groups, or combined.

The assigned diets were fed, on average, for only the first 4 weeks of life. After this period children were fed as their parents chose. Surviving children were assessed at 18 months post term using the mental and motor scales of the Bayley scales of infant development.\textsuperscript{30}

Study 2, the comparison between term and preterm formula, was completed first. In the group fed the milks as their sole diet, the PDI advantage for those fed preterm formula was 14.7 points. The effect of diet on development was greatest in children born small for gestation age and in males, in both of these subgroups there were significant advantages in both the Bayley Mental Development Index (MDI) and PDI, with significant interactions between diet and both size for gestation and sex.

Enteral intake in these preterm infants was variable, with some children needing prolonged intravenous feeding. When only those children who had received the assigned milk for at least 2 weeks were included in analyses, there were significant and larger developmental advantages in both MDI and PDI for those fed preterm rather than term formula. In children fed the allocated milk as their \textit{sole diet} for at least 2 weeks the advantages were 9 points ($P < 0.05$) and 15 points ($P < 0.01$), respectively.

Preliminary (unpublished) data suggest that the effect of diet on performance, especially in verbal IQ and in male children, is persisting to 7.5–8 years, when cognitive function is highly predictive of that in adulthood.

\textbf{Breast milk:} In study 1 (see Fig. 1), a unique group of children were randomly allocated human breast milk. The milk was fed by nasogastric tube to infants whose mothers had chosen \textit{not} to provide their own breast milk. The two major potential areas of confounding were avoided in this study because all the mothers had chosen not to provide breast milk, avoiding social and demographic confounding and since the infants were fed by nasogastric tube the human milk fed group were not exposed to the influence of intimacy with the mother during breast feeding. In a comparison of infants fed donor milk with those fed standard term formula (from two parallel trials and all with mothers who had chosen not to provide breast milk), the human milk group had significantly higher PDI.\textsuperscript{31} Furthermore, despite substantial nutrient differences between the banked donor milk and preterm formula, there was no advantage for the preterm formula fed group. These findings contrast sharply with those from study 2 (preterm versus preterm formula comparison) and lend weight to the hypothesis that human milk does contain a factor or factors which promote neurodevelopment and
ameliorate the adverse effects of poor nutrition. Candidate factors include the range of biologically active peptides in milk, (including nerve growth factor and insulin-like growth factors). The extent to which these reach target tissues in the infant and whether they are important for brain development is not understood.

Human milk also contains a range of long chain polyunsaturated fatty acids (LCPUFAs), notably docosahexaenoic acid (DHA, 22:6ω3), whereas conventional formulas contain a negligible amount. The brain and retina are rich in DHA and there is considerable interest in whether the DHA available to the infant from human milk might be the explanation, at least in part, for the developmental advantage generally associated with breast feeding. A number of studies have been undertaken to investigate whether DHA supplementation of formula milk promotes development in term or preterm infants.

**Polyunsaturated fatty acids**

The brain and retina are rich in both DHA and arachidonic acid (AA) and uptake by these tissues increases substantially during the last trimester of pregnancy and for several months after birth. There is good evidence that the DHA content of the infant's diet is reflected in the composition of the infant's tissues.

To date there are few published data on the influence of LCPUFA supplementation on developmental status and most studies have been too small to provide convincing evidence. The issue of whether dietary long chain polyunsaturated fatty acids in infancy confer a cognitive advantage and are at least part of the explanation for the generally found advantage for breast fed subjects is as yet unresolved. The results of current large randomised trials of dietary LCPUFA are awaited with interest.

**Dietary iron**

Iron deficiency anaemia is considered the most common nutritional deficiency disease in infants and children in the West, with around 10% of children affected, and its prevalence has been estimated at around 50% in less developed countries, where it is associated with poverty, malnutrition and disease, especially parasitic infections. Iron supplementation of milk formulas or weaning foods has been shown to reduce the incidence of iron deficiency anaemia in the West. Evidence from observational studies suggests that children with iron deficiency anaemia suffer a developmental disadvantage, so supplementation is most likely
to be beneficial in this group. However, there are ethical difficulties in randomising anaemic children to iron supplementation or placebo.

In most of the intervention trials (mainly conducted in less developed countries) there was no evidence of developmental benefit from iron supplementation\textsuperscript{11}, though the interventions were generally very short. In a study of healthy formula fed infants from very low income families in the West (a high risk group for iron deficiency anaemia) those randomly assigned iron fortified rather than standard formula had significantly higher Bayley motor scale scores than the controls at 9 and 12 months\textsuperscript{41}. The effect did not persist to 18 months, but 46\% of subjects had dropped out of the study, raising the possibility of selection bias. Positive evidence for the importance of iron in development comes from a randomised trial conducted by Idjradinata et al\textsuperscript{42}. Children aged 12–18 months with iron deficiency anaemia were randomly allocated a placebo or ferrous sulphate. The children given 3 mg/kg of ferrous sulphate per day showed marked improvements in both Bayley MDI and PDI after 4 months of treatment, whereas there was no significant change in the scores of the placebo group. Although the number of subjects was small, great care was taken to investigate the possibility of confounding, which in any case could be expected to have a less powerful influence on change in scores. Longer term follow up data are required to determine whether any benefits from early iron supplementation persist beyond the intervention period in infancy.

**Overview**

The importance of early nutrition for later cognitive development continues to be debated. Previous studies of malnourished babies in developing countries may sometimes have been motivated by political needs to stimulate aid programmes, though it should be unnecessary to prove that malnutrition damages a baby’s brain in order to provide a stimulus to reduce poverty and hunger.

However, despite many studies that have related early undernutrition to later cognitive deficits, extensive reviews\textsuperscript{43–45} of this body of work have suggested that most studies were too confounded by flaws in design to provide compelling evidence. More recently, however, tightly designed nutritional intervention studies have provided new and more convincing evidence that the brain may be vulnerable to suboptimal nutrition in early life. For instance, the new randomised trials of early nutrition in preterm babies suggest that nutrition prior to full term may have profound later effects, with major implications for clinical practice.

But there is still much that remains unresolved: does breast feeding really
make children brighter? Should long chain lipids be added to infant formulas? Is iron deficiency, so prevalent worldwide, really a significant hazard for cognitive development? The intense focus on these issues and the new understanding of the importance of conducting studies with strict experimental design is likely to provide much better answers than we have had so far.

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