Nutritional deficiencies and later behavioural development

S. M. Grantham-McGregor1*, S. P. Walker2 and S. Chang2
1Centre for International Child Health, Institute of Child Health, 30 Guilford St, London WCI IEH, UK
2Tropical Metabolism Research Unit, University of the West Indies, Jamaica

The literature on the long-term effects of nutritional deficiencies in early life is reviewed. The severity and duration of the deficiency, the stage of the children’s development, the biological condition of the children and the socio-cultural context may all modify the effect. There is substantial evidence that reduced breast-feeding, small-for-gestational-age birth weight, Fe and I deficiency, and protein–energy malnutrition (PEM) are associated with long-term deficits in cognition and school achievement. However, all these conditions are associated with poverty and poor health, which may account for the association. It is difficult to establish that the long-term relationship is causal, as it requires a randomized treatment trial with long-term follow-up. Such studies are only available for I deficiency in utero and early childhood PEM. Results from these studies indicate that I deficiency has a long-term effect and PEM probably has a long-term effect.

**Child development: Nutrient deficiencies**

There is now evidence linking many nutritional deficiencies to deficits in cognition, motor performance and behaviour. These conditions include low birth weight due to under-nutrition, early childhood protein–energy malnutrition (PEM), deficiencies of I, Fe and Zn, short-term food deprivation, insufficient essential fatty acids and inadequate breast-feeding. The effects may be transient, last for a longer time or be permanent.

**Factors influencing the impact**

The severity of the deficiency and the stage of development of the subject may influence the impact. A clear example of the importance of the stage of development is the effect of I deficiency in early pregnancy. Not only does cretinism result from severe I deficiency in early pregnancy, but also reduced levels of development follow deficiency in the first two trimesters compared with the third trimester (Cao et al. 1994). It is suspected that duration of the deficiency is important, but the evidence is limited. In a Chilean study, Walter et al. (1989) found that children who had been anaemic for the longest period of time had the poorest development. It is also clear that wasting is not such a consistent predictor of poor development as stunting which takes longer to develop (Grantham-McGregor et al. 1999). However, other factors play a role in the aetiology of stunting and wasting. There are several data sets from old longitudinal studies that could be used to examine the effect of duration in more detail.

Other factors including the economic and socio-cultural environment, and the biological state of the child also modify the effect of the deficiency, and indeed may determine whether there is an effect at all. Most attention has been paid to socio-cultural and economic conditions, because it is well established that nutritional deficiencies are more likely to occur in circumstances of poverty and illiteracy. For example, low-birth-weight term babies living in homes with poor levels of stimulation in Brazil had much lower levels of development than normal-birth-weight babies from similar homes. In contrast, in homes with better levels of stimulation, the difference between the groups was small (Grantham McGregor et al. 1998). Similarly, in homes with illiterate mothers low-birth-weight term babies had much poorer levels of development than normal-birth-weight babies from similar homes. In contrast, in homes with better levels of stimulation, the difference between the groups was much less in babies of literate mothers. Analogously, the development of children who live in middle-class homes is less likely to be affected by severe malnutrition in early childhood than the development of children living in poverty (Rush, 1984). A further example of the effect of the environment is that nutritional supplementation has a greater benefit on the long-term development of children from the poorer homes (Pollitt et al. 1993).

**Abbreviations:** IQ, intelligence quotient; PEM, protein–energy malnutrition; SGA, small-for-gestational age.

*Corresponding author: Dr S. M. Grantham-McGregor, fax +44 (0)207 831 0488, email smcgregor@ich.ucl.ac.uk
The moderating effect of the biological state of the child has received less attention; however, there is evidence that the effect of low birth weight is worse in babies with frequent diarrhoea (Morris et al. 1999). Similarly, the effect of short-term food deprivation on cognition is worse in undernourished children than in adequately-nourished children (Simeon & Grantham McGregor, 1990).

In the present paper we will discuss evidence of long-term effects of nutritional deficits on children’s development, but will not discuss concurrent effects. We will focus mainly on PEM, but will discuss other nutrients briefly. We are unaware of any studies of the long-term effects of Zn deficiency or repeated short-term food deprivation.

Small-for-gestational age

Hack (1998) identified twelve longitudinal observational studies of children between 9 and 17 years of age who were small-for-gestational age (SGA) at birth (Drillien, 1970; Hill, 1978; Westwood et al., 1983; Ilsey & Mitchell, 1984; Rantakilii, 1988; Hawdon et al., 1990; Lagerstrom et al., 1991; Low et al., 1992; Agarwal et al., 1995; Mervis et al., 1995; Paz et al., 1995; Pryor et al., 1995). In all studies the SGA babies had poorer cognition than normal-birth-weight children, although some of the differences were not statistically significant (for example, see Hawdon et al., 1990; Agarwal et al., 1995). The results of these studies are shown in Fig. 1. In most of the studies the SGA children also had poorer school performance levels. Only one of the twelve studies was from a developing country (Agarwal et al., 1995), and early childhood malnutrition had a greater effect than SGA. An additional study from Guatemala (Perez-Escamilla & Pollitt, 1992) failed to find any cognitive deficit at adolescence in SGA children. It is possible that extremely poor early childhood health and nutrition overwhelms the effect of SGA.

Studies of slightly younger SGA children have shown that schoolchildren tend to have poor attention span, be more anxious and fidgety, and less happy than controls (Grantham-McGregor, 1998). Few studies have examined adults, and the findings have been inconsistent, often with a large loss of subjects from follow-up (Hack, 1998).

Breast-feeding

In a previous review (Grantham-McGregor et al. 1999) we found fourteen studies evaluating the long-term effect of breast-feeding on cognitive development, with the subjects at follow-up aged from 4 to 50 years old (Hoefer & Hardy, 1929; Rodgers, 1978; Fergusson et al., 1982; Ounsted et al., 1984; Taylor & Wadsworth, 1984; Jacobson & Jacobson, 1992; Lucas et al., 1992; Rogan & Gladen, 1993; Gale & Martyn, 1996; Niemela & Jarvenpaa, 1996; Horwood & Fergusson, 1998; Malloy & Berendes, 1998). In all the studies the breast-fed group showed a consistent small benefit compared with a non-breast-fed group, although the difference was not always significant. The size of the effect was small and averaged approximately 0.22 of a standard score of the test used (Fig. 2). A few of the studies examined reading ability or school attainment, and breast-fed children tended to do better (for example, see Rodgers, 1978; Ounsted et al., 1984; Rogan & Gladen, 1993; Horwood & Fergusson, 1998), although not always (Pollock, 1994). Children’s behaviour has been examined infrequently and the findings are inconsistent (Taylor & Wadsworth, 1984; Fergusson et al., 1987). We found only one treatment trial of breast-feeding, and in that trial low-birth-weight babies were randomly assigned to breast milk or preterm formula for a short time. The children who were fed with breast milk

Fig. 1. Intelligence quotient (IQ) score of small-for-gestational-age (■) and normal-birth-weight (□) children in early adolescence. (Based on Hack, 1998.)
were not different from those who were given preterm formula, although they had better mental development than children in a parallel study of children who received term formula (Morley & Lucas, 1994).

It is possible that any benefit from breast-feeding is due to the unique nutritional content, and most research has focused on the role of essential fatty acids (Uauy et al., 1992). However, improved maternal child interaction and reduced morbidity could account for the effect or contribute to it. In addition, mothers who breast-feed are usually different from mothers who do not, and control for these differences has often been inadequate.

Iron deficiency

There are four long-term studies of children who had Fe-deficiency anaemia in the first 2 years of life. These studies were conducted in Costa Rica (Lozoff et al., 1991), Chile (de Andraça et al., 1990), Israel (Palti et al., 1985) and the USA (Cantwell, 1974). The children were treated at the time of anaemia; however, in all studies the previously-anaemic children showed deficits in cognitive function. The studies from Costa Rica and Chile found that the formerly-anaemic children showed deficits in a wide range of cognitive, motor and psycho-educational tests compared with non-anaemic children. No study included anaemic children which had been randomly assigned to placebo.

Iodine deficiency

Many studies have compared children living in I-deficient areas with those living in I-sufficient areas, and generally the I-deficient children have had poorer levels of cognitive development and school achievement (Fernald & Grantham McGregor, 1998). However, it is not possible to separate the effects of intra-uterine deficiency from those of continuing deficiency throughout childhood.

Protein–energy malnutrition

Most early research on nutrition and mental development concerned severe PEM, and there are many follow-up studies of school-aged children who were hospitalized for marasmus, kwashiorkor or marasmic kwashiorkor in early childhood. Many of the early studies lacked suitable controls. In a recent review (Grantham McGregor, 1995) fourteen studies were identified in which the children were compared with reasonably-well-matched controls or siblings. In most of the studies the formerly-malnourished children had poorer cognitive function and school achievement, and behaviour differences compared with the controls. Where differences were not found they tended to involve sibling comparisons and use school achievement
measures. Although siblings may be a good match for environmental conditions, they are likely to have been undernourished themselves, thereby reducing the chance of showing differences from the index child. Formerly-severely-malnourished children have also been shown to have neurological soft signs and poorer fine motor performance (Galler et al. 1984). The reports of their parents and teachers indicate that they make poor relationships with peers and adults, and have poorer attention (Grantham McGregor, 1995).

It appears that the long-term outcome of severe PEM depends largely on the subsequent quality of the children’s environment. Several studies of children who were adopted into more affluent homes have shown that vast improvements in development can take place (Winick et al. 1975; Colombo et al. 1992). A small study of psychosocial stimulation, which comprised home visiting with play demonstrations, also showed sustained benefits on the children’s development (Grantham McGregor et al. 1994).

Conclusions from longitudinal studies

The findings from the longitudinal observational studies of low-birth-weight, breast-feeding, Fe and I deficiency and severe PEM suggest that there is a long-term effect on children’s development from the nutritional insult (or advantage in breast-feeding). However, it is impossible to infer a causal relationship with certainty, because other factors which are associated with nutritional deficits may explain the findings. Many socio-economic and cultural factors affect development and, although most of the investigators controlled for at least some social background factors, other unmeasured factors may account for the results. In order to demonstrate a long-term effect, randomized controlled trials are needed, and we could only find long-term follow-up studies of trials concerning I and PEM.

Iodine-supplementation trials

In two I-supplementation trials in pregnancy the children were followed-up in later childhood. In Equador pregnant women were supplemented in one village but not another (Greene, 1994). The children born to I-supplemented women had better school achievement levels and IQ scores between 8 and 15 years of age than those born to non-supplemented women. However, there were only two villages, and they are unlikely to be the same in all factors affecting mental development.

A randomized controlled trial of I supplementation in Papua New Guinea clearly showed a reduction in cretinism (Pharoah et al. 1971). The children were followed up to 10 years of age, when the supplemented group had better fine motor skills (Connolly et al. 1979). It was also shown that when the children were 14–16 years of age their performance on some cognitive function tests was related to their mothers’ thyroxine levels in pregnancy (Connolly & Pharoah, 1989). There is therefore good evidence of an effect on cretinism, and limited evidence of a long-term effect on motor and cognitive function following preventive supplementation.

Trials of preventive supplementation (protein–energy malnutrition)

Several early supplementation trials were conducted in areas where PEM was endemic and high-risk mothers were supplemented from pregnancy. These trials were conducted in Mexico (Chavez & Martinez, 1982), Guatemala (Freeman et al. 1980), Bogota, Colombia (Waber et al. 1981) and Taiwan (Joos et al. 1983). Concurrent benefits to the children’s development were found in each trial. In Taiwan the mothers were supplemented in pregnancy and lactation, but the children were not supplemented, and no benefit was found to the children’s IQ at 5 years of age. In the other three studies the children were also supplemented for at least 3 years and long-term benefits were reported from each study (Pollitt et al. 1993; Chavez et al. 1994; C Super and MG Herrera, unpublished results). However, details from the Bogota study have not been reported (C Super and MG Herrera, unpublished results), and the samples in the Mexican study were small and children were not assigned to treatment groups by randomization but were separated by time.

In Guatemala (Pollitt et al. 1993) children in two villages received high-energy high-protein supplementation (atole) and the children in two other villages received a low-energy drink (fresco). At adolescence, the children in the ‘atole’ villages had higher scores in tests of numeracy, knowledge, vocabulary and reading, and the benefits were mostly found in the children from the poorest homes (Fig. 4). These findings suggest a causal relationship. However, the randomization in the Guatemalan study was by villages (n 4), and there were differences between the ‘atole’ and ‘fresco’ villages in a number of critical socio-cultural variables, despite initial matching.

Trials of remedial supplementation

Three remedial supplementation studies have been conducted in children who were already undernourished, in Jamaica (Grantham McGregor et al. 1991), Colombia (McKay et al. 1978) and Indonesia (Husaini et al. 1991), and they were all randomized controlled trials. In Indonesia and Jamaica children showed concurrent benefits from supplementation alone. In the third study (McKay et al. 1978) benefits were found from supplementation combined with stimulation, but not from supplementation alone. In Indonesia benefits were limited to motor development (Husaini et al. 1991). In the Jamaican study (Grantham McGregor et al. 1991) there were four groups of children: supplemented; stimulated; both treatments combined; controls. Stimulation and supplementation had independent benefits on the children’s development and the effects were additive. The group receiving both treatments caught up to an adequately-nourished comparison group which was also being studied.

On long-term follow-up, children in the Colombian study showed sustained benefits from combined stimulation
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and supplementation through the first three school grades (McKay & McKay, 1983). In Indonesia (Pollitt et al. 1997), benefits in one test of memory were reported, but only in children supplemented before 18 months of age. In Jamaica, small global benefits were found at 7 years of age from all interventions, but there was no longer an additive effect (Grantham McGregor et al. 1997).

Preliminary analysis of data collected at 11 years of age shows that there is no longer a benefit from supplementation, but a clear benefit from stimulation remained (S Walker, S Grantham-McGregor, S Chang and C Powell, unpublished results).

Conclusions from intervention trials (protein–energy malnutrition)

In spite of many design problems the evidence is extremely consistent, that in populations where undernutrition is endemic supplementation given preventively in pregnancy and in the first 3 years of life benefits children’s concurrent development. There is some evidence of a long-term effect, but more studies would be helpful.

There are only two studies (Grantham McGregor et al. 1991; Husaini et al. 1991) in which undernourished children showed concurrent benefits from supplementation. In one of these studies benefits were sustained but only in children who were under 18 months of age at the time of supplementation (Pollitt et al. 1997). It may be that continued supplementation is needed for benefits to be sustained, or that there is a vulnerable period when the undernutrition is most likely to have a sustained effect.

In order to explore the possibility of a vulnerable period, we examined the relationship between nutritional indices assessed at different ages in a group of stunted children and their IQ measured at 11 years of age (S Walker, S Grantham-McGregor, S Chang and C Powell, unpublished results). The indices were head circumference, height and weight-for-height, which were measured on enrolment to the study when the children were between 9 and 24 months of age, then 2, 4 and 8 years later, at which time they were 11–12 years of age. Several multiple regression analyses were conducted predicting IQ. In separate analyses each anthropometric measure taken at each age was offered after controlling for sex, age and socio-economic variables. Head circumference on enrolment predicted IQ more strongly than head circumference 2 years later, and head circumference at the older ages was not a significant predictor. Height on enrolment was the only height measure to predict IQ. Weight-for-height was not a significant predictor of IQ at any age. These analyses indicate that head circumference and height in the first 24 months of life were more significant predictors of IQ at 11 years of age than more recent or concurrent measures, and one explanation could be that children at the younger age are more vulnerable to the effects of undernutrition.

Mechanism linking protein–energy malnutrition to development

The mechanism linking PEM to poor development is not known with certainty; however, several different mechanisms have been suggested (Levitsky & Strupp, 1995). One mechanism is through changes to the brain’s anatomy or function. Another mechanism is known as ‘the functional isolation hypothesis’, and concerns undernourished children’s behaviour. The children have reduced activity and exploration, and it is thought that this process leads to their acquiring skills more slowly. Also their caregivers become less stimulating in response to the children’s behaviour, which may exacerbate the problem.

We recently found that stunted children aged 8–10 years old were more inhibited than non-stunted children when placed in a stressful situation. They also had increased levels of cortisol (Fig. 5) and heart rates (Fernald & Grantham McGregor, 1998). It may be that the stress response of undernourished young children is altered, and that these changes are sustained. Altered stress response could contribute to the children’s behavioural differences. It has been shown that inhibited adequately-nourished children have higher cortisol levels.
Overall conclusions

We have reviewed the long-term effects of nutrient deficiencies in childhood. There is now considerable evidence that SGA births, reduced breast-feeding, Fe deficiency, severe and moderate PEM in early childhood, and I deficiency in utero are associated with long-term deficits in cognitive and motor function, and poor school achievement levels. Behaviour differences have also been found in long-term follow-up studies of children who had PEM. However, the evidence that these relationships are causal is extremely difficult to collect, and requires long-term follow-up studies of randomized controlled trials. Such studies are only available for PEM in early childhood and I deficiency in utero. Results from these studies indicate that I deficiency in utero has a long-term effect, and that PEM in early childhood probably has a long-term effect.

References


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