Nutritional deficiencies and later behavioural development

S. M. Grantham-McGregor[1]*, S. P. Walker[2] and S. Chang[2]
[1]*Centre for International Child Health, Institute of Child Health, 30 Guilford St, London WCI IEH, UK*
[2]*Tropical 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, and 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

https://doi.org/10.1017/S0029665100000069 Published online by Cambridge University Press

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; Illsey & Mitchell, 1984; Rantakillio, 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

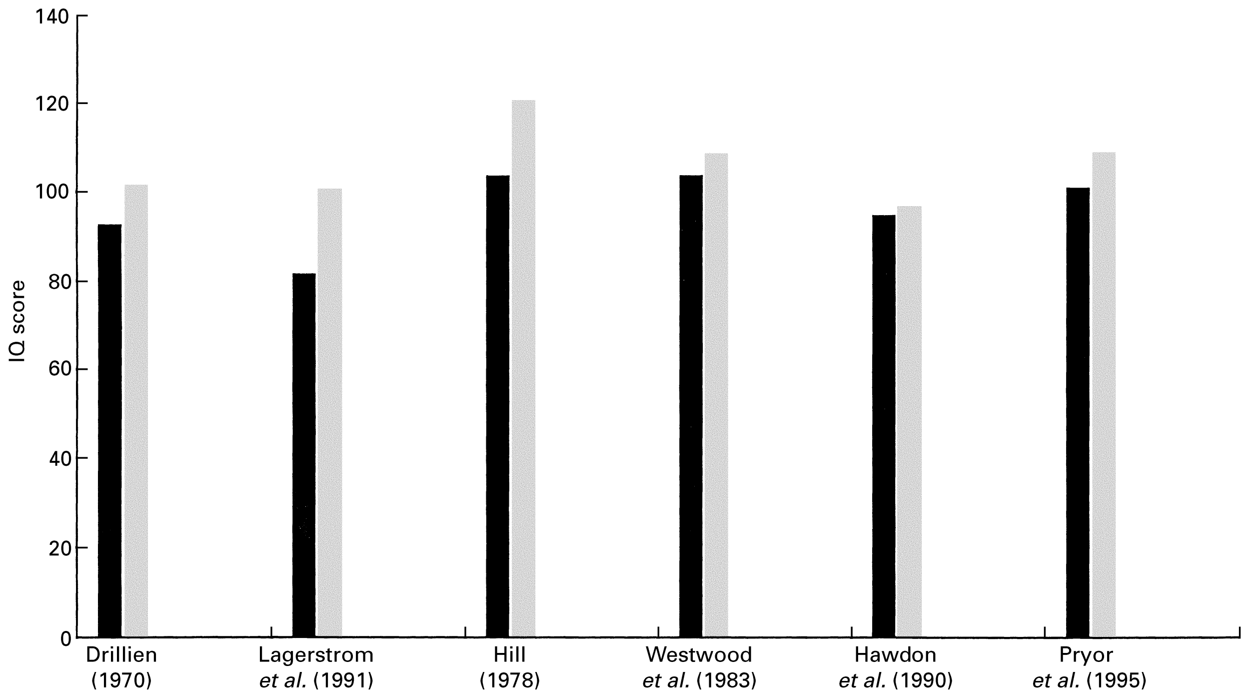

Fig. 1. Intelligence quotient (IQ) score of small-for-gestational-age (■) and normal-birth-weight (▒) children in early adolescence. (Based on Hack, 1998.)

https://doi.org/10.1017/S0029665100000069 Published online by Cambridge University Press

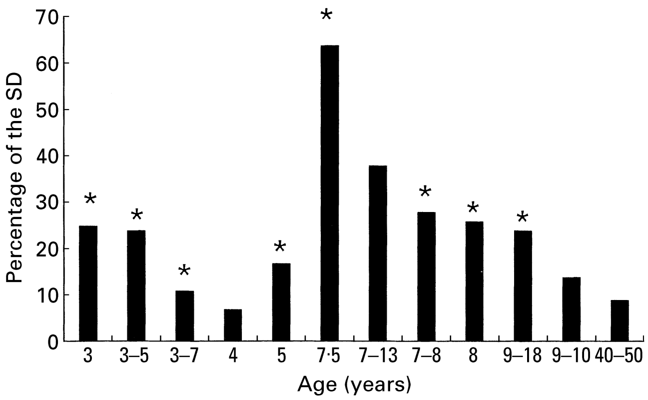

Fig. 2. Differences between breast-fed and non-breast-fed babies in standard scores (SD) of the cognitive test used in the study. Data were taken from Niemala & Jarvenpaa (1996), Rogan & Gladen (1993), Fergusson *et al.* (1982), Jacobson & Jacobson (1992), Taylor & Wadsworth (1984), Ounsted *et al.* (1984), Hoefer & Hardy (1929), Lucas *et al.* (1992), Rodgers (1978), Horwood & Fergusson (1998), Malloy & Berendes (1998) and Gale & Martyn (1996). *Studies which adjusted for socio-economic status. (Adapted from Grantham-McGregor *et al.* 1999.)

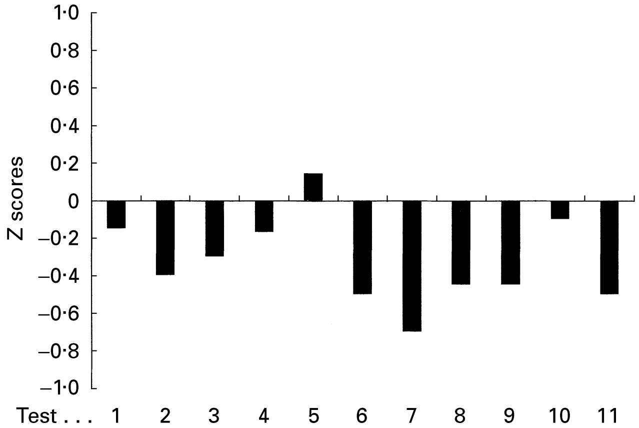

Fig. 3. Developmental disadvantage in cognitive, motor and psycho-educational tests in children at 5 years of age who had iron-deficiency anaemia in infancy. Values are means for 191 subjects. 1, Draw-a-man; 2, the Beery Developmental Test of visual–motor integration; 3–7, the Woodcock-Johnson Psycho-educational Battery (3, picture vocabulary; 4, spatial relations; 5, visual–auditory; 6, quantitative concepts; 7, visual matching); 8, gross motor; 9, fine motor; 10, verbal intelligence quotient; 11, performance quotient. (Adapted from Lozoff *et al.* 1991.)

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 Andraca *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. Fig. 3 shows the deficits found in the Chilean study. The formerly-anaemic children in Israel (Palti *et al.* 1983, 1985) had lower intelligence quotient (IQ) scores and poorer school grades. In one of the studies (Cantwell, 1974) the anaemic children were reported to have a lower IQ and more neurological soft signs, but no details were given. In a further study (EK Hurtado, AH Claussen and KG Scott, personal communication) the records of a government nutritional supplementation programme in Florida, USA were examined, and children who were anaemic (presumed to be due to Fe deficiency) on enrolment in the first 4 years of life were identified. The school records of these children were traced and they were more likely to be in special education classes, implying mild to moderate mental retardation, than other participants in the programme.

We could not find a report of the children's behaviour, although concurrent anaemia is associated with marked behaviour differences in infants (Lozoff, 1998). Although the children in these studies had been given Fe treatment, all comparisons were 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

https://doi.org/10.1017/S0029665100000069 Published online by Cambridge University Press

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 pyschosocial 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

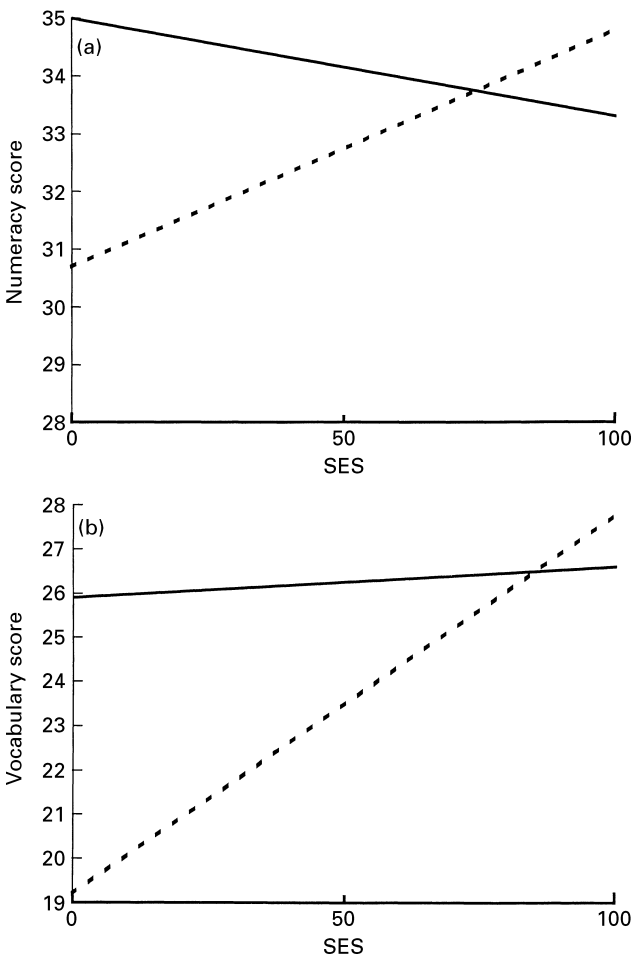

Fig. 4. (a) Numeracy and (b) vocabulary scores in adolescents who received high-energy high-protein supplement (atole; ——) and low-energy drink (fresco; - - - -) in early childhood relative to socio-economic status (SES). (Adapted from Pollitt *et al.* 1993.)

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 supplemention. 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.

Vulnerable period

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.

https://doi.org/10.1017/S0029665100000069 Published online by Cambridge University Press

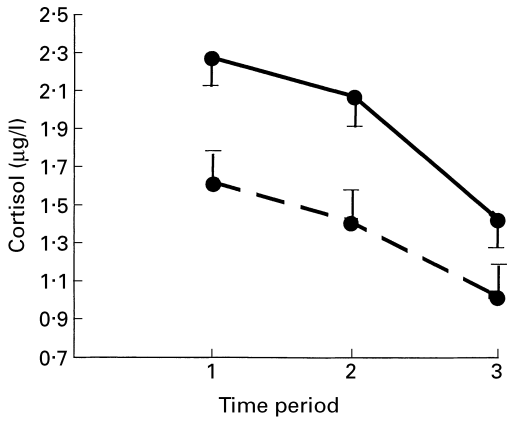

Fig. 5. Cortisol levels over three time periods (1, baseline; 2, mid test; 3, post test) in stunted (—) and non-stunted (– –) children aged 8–10 years old. Values are geometric means and 95% CI. (Adapted from Fernald & Grantham-McGregor, 1998.)

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

Agarwal KN, Agarwal DK & Upadhyay SK (1995) Impact of chronic undernutrition on higher mental functions in Indian boys aged 10–12 years. *Acta Paediatrica* **84**, 1357–1361.

Cantwell RJ (1974) The long term neurological sequelae of anemia in infancy. *Pediatric Research* **342**, 68.

Cao XY, Jiang X-M, Dou Z-H, Murdon AR, Zhang M-L, O'Donnell K, Tai M, Amette K, DeLong N & Delong GR (1994) Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *New England Journal of Medicine* **331**, 1739–1744.

Chavez A & Martinez C (1982) *Growing Up In a Developing Community*. Guatemala City: Institute of Nutrition in Central America and Panama.

Chavez A, Martinez C, Soberanes B, Dominguez L & Avila A (1994) *Early Nutrition and Physical and Mental Development in Mexican Rural Adolescent Families*. Washington, DC: International Center for Research on Women.

Colombo M, de la Parra A & Lopez I (1992) Intellectual and physical outcome of children undernourished in early life is influenced by later environmental conditions. *Developmental Medicine and Child Neurology* **34**, 611–622.

Connolly KJ & Pharoah POD (1989) Iodine deficiency, maternal thyroxine levels in pregnancy and developmental disorders in the children. In *Iodine and the Brain*, pp. 317–331 [GR Delong, J Robbins and PG Condliffe, editors]. New York: Plenum Press.

Connolly KJ, Pharaoh POD & Hetzel BS (1979) Fetal iodine deficiency and motor performance during childhood. *Lancet* **ii**, 1149–1151.

de Andraca I, Walter T, Castillo M, Pino P, Rivera P & Cobo C (1990) Iron deficiency anemia and its effects upon psychological development at preschool age: a longitudinal study. *Nestle Foundation Annual Report*, pp. 53–62. Lausanne: Nestle Foundation.

Drillien CM (1970) The small-for-date infant: etiology and prognosis. *Pediatric Clinics of North America* **17**, 9–24.

Fergusson DM, Beautrais AL & Silva PA (1982) Breast-feeding and cognitive development in the first seven years of life. *Social Science and Medicine* **16**, 1705–1708.

Fergusson DM, Horwood LJ & Shannon FT (1987) Breastfeeding and subsequent social adjustment in six- to eight-year-old children. *Journal of Child Psychology and Psychiatry* **28**, 379–386.

Fernald LC & Grantham McGregor SM (1998) Stress response in school-age children who have been growth retarded since early childhood. *American Journal of Clinical Nutrition* **68**, 691–698.

Freeman HE, Klein RE, Townsend JW & Lechtig A (1980) Nutrition and cognitive development among rural Guatemalan children. *American Journal of Public Health* **70**, 1277–1285.

Gale CR & Martyn CN (1996) Breastfeeding, dummy use, and adult intelligence. *Lancet* **347**, 1072–1075.

Galler JR, Ramsey F, Solimano G, Kucharski LT & Harrison R (1984) The influence of early malnutrition on subsequent behavioral development. IV. Soft neurologic signs. *Pediatric Research* **18**, 826–832.

Grantham McGregor S (1995) A review of studies of the effect of severe malnutrition on mental development. *Journal of Nutrition* **125**, 2233S–2238S.

Grantham-McGregor SM (1998) Small for gestational age, term babies, in the first six years of life. *European Journal of Clinical Nutrition* **52**, S59–S64.

Grantham-McGregor SM, Fernald LC & Sethuraman K (1999) The effects of health and nutrition on cognitive and behavioural development in children in the first three years of life. Part 1: Low birthweight, breast feeding and protein energy malnutrition. *Food and Nutrition Bulletin* **20**, 53–75.

Grantham McGregor SM, Lira PI, Ashworth A, Morris SS & Assuncao AM (1998) The development of low birth weight term infants and the effects of the environment in northeast Brazil. *Journal of Pediatrics* **132**, 661–666.

Grantham McGregor SM, Powell CA, Walker SP & Himes JH (1991) Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. *Lancet* **338**, 1–5.

Grantham McGregor S, Powell C, Walker S, Chang S & Fletcher P (1994) The long-term follow-up of severely malnourished children who participated in an intervention program. *Child Development* **65**, 428–439.

Grantham McGregor SM, Walker SP, Chang SM & Powell CA (1997) Effects of early childhood supplementation with and without stimulation on later development in stunted Jamaican children. *American Journal of Clinical Nutrition* **66**, 247–253.

Greene LS (1994) A retrospective view of iodine deficiency, brain development and behavior from studies in Ecuador. In *The Damaged Brain of Iodine Deficiency*, pp. 173–186 [JB Stanbury, editor]. New York: Cognizant Communication.

Hack M (1998) Effects of intrauterine growth retardation on mental performance and behavior: outcomes during adolescence and adulthood. *European Journal of Clinical Nutrition* **52**, S65–S71.
Hawdon J, Hey E, Kolvin I & Fundudis T (1990) Born too small – is outcome still affected? *Developmental Medicine and Child Neurology* **32**, 943–953.
Hill DE (1978) Physical growth and development after intrauterine growth retardation. *Journal of Reproductive Medicine* **21**, 335–342.
Hoefer C & Hardy MC (1929) Later development of breast fed and artificially fed infants: comparison of physical and mental growth. *Journal of the American Medical Association* **92**, 615–619.
Horwood LJ & Fergusson DM (1998) Breastfeeding and later cognitive and academic outcomes. *Pediatrics* **101**, E9.
Husaini MA, Karyadi L, Husaini YK, Sandjaja, Karyadi D & Pollitt E (1991) Developmental effects of short-term supplementary feeding in nutritionally-at-risk Indonesian infants. *American Journal of Clinical Nutrition* **54**, 799–804.
Illsey R & Mitchell RG (1984) *Low Birth Weight: A Medical, Psychological and Social Study*. Chichester: John Wiley & Sons.
Jacobson SW & Jacobson JL (1992) Breastfeeding and intelligence. *Lancet* **339**, 926.
Joos SK, Pollitt E, Mueller WH & Albright DL (1983) The Bacon Chow study: maternal nutritional supplementation and infant behavioral development. *Child Development* **54**, 669–676.
Lagerstrom M, Bremme K, Eneroth P & Magnusson D (1991) School performance and IQ-test scores at age 13 as related to birth weight and gestational age. *Scandinavian Journal of Psychology* **32**, 316–324.
Levitsky DA & Strupp BJ (1995) Malnutrition and the brain: changing concepts, changing concerns. *Journal of Nutrition* **125**, 2245S–2254S.
Low JA, Handley-Derry MH, Burke SO, Peters RD, Pater EA, Killen HL & Derrick EJ (1992) Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *American Journal of Obstetrics and Gynecology* **167**, 1499–1505.
Lozoff B (1998) Explanatory mechanisms for poorer development in iron-deficient anemic infants. In *Nutrition, Health and Child Development: Research Advances and Policy Recommendations*, pp. 162–178 [SM Grantham-McGregor, editor]. Washington, DC: PAHO.
Lozoff B, Jimenez E & Wolf AW (1991) Long-term developmental outcome of infants with iron deficiency. *New England Journal of Medicine* **325**, 687–694.
Lucas A, Morley R, Cole TJ, Lister G & Leeson Payne C (1992) Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* **339**, 261–264.
McKay A & McKay H (1983) Primary school progress after preschool experience: troublesome issues in the conduct of follow up research and findings from the Cali, Columbia, study. In *Preventing School Failure: The Relationship Between Preschool and Primary Education*, pp. 36–41. Ottawa, Ont.: International Development Research Centre.
McKay H, Sinisterra L, McKay A, Gomez H & Lloreda P (1978) Improving cognitive ability in chronically deprived children. *Science* **200**, 270–278.
Malloy MH & Berendes H (1998) Does breast-feeding influence intelligence quotients at 9 and 10 years of age? *Early Human Development* **50**, 209–217.
Mervis CA, Decoufle P, Murphy CC & Yeargin-Allsopp M (1995) Low birthweight and the risk for mental retardation later in childhood. *Pediatric Perinatal Epidemiology* **9**, 455–468.
Morley R & Lucas A (1994) Influence of early diet on outcome in preterm infants. *Acta Paediatrica* **405**, Suppl., 123–126.
Morris SS, Grantham-McGregor SM, Lira PIC, Assunçâo AMS & Ashworth A (1999) Breastfeeding, morbidity, birth weight and infant development. *Acta Paediatrica* (In the Press).
Niemela A & Jarvenpaa AL (1996) Is breastfeeding beneficial and maternal smoking harmful to the cognitive development of children? *Acta Paediatrica* **85**, 1202–1206.
Ounsted M, Moar VA, Cockburn J & Redman CW (1984) Factors associated with the intellectual ability of children born to women with high risk pregnancies. *British Medical Journal of Clinical Research and Education* **288**, 1038–1041.
Palti H, Meijer A & Adler B (1985) Learning achievement and behavior at school of anemic and non-anemic infants. *Early Human Development* **10**, 217–223.
Palti H, Pevsner B & Adler B (1983) Does anemia in infancy affect achievement on developmental and intelligence tests? *Human Biology* **55**, 183–194.
Paz I, Gale R, Laor A, Danon YL, Stevenson DK & Seidman DS (1995) The cognitive outcome of full-term small for gestational age infants at late adolescence. *Obstetrics and Gynecology* **85**, 452–456.
Perez-Escamilla R & Pollitt E (1992) Causes and consequences of intrauterine growth retardation in Latin America. *Bulletin of the Pan American Health Organization* **26**, 128–146.
Pharoah POD, Buttfield IH & Hetzel BS (1971) Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* **i**, 308–310.
Pollitt E, Gorman KS, Engle PL, Martorell R & Rivera J (1993) Early supplementary feeding and cognition. *Monographs of the Society for Child Development* **58**.
Pollitt E, Watkins WE & Husaini MA (1997) Three-month nutritional supplementation in Indonesian infants and toddlers benefits memory function 8 y later. *American Journal of Clinical Nutrition* **66**, 1357–1363.
Pollock JI (1994) Long-term associations with infant feeding in a clinically advantaged population of babies. *Developmental Medicine and Child Neurology* **36**, 429–440.
Pryor J, Silva PA & Brooke M (1995) Growth, development and behaviour in adolescents born small-for-gestational-age. *Journal of Paediatrics and Child Health* **31**, 403–407.
Rantakillio P (1988) The longitudinal study of the Northern Birth cohort of 1966. *Paediatric Perinatal Epidemiology* **2**, 59–88.
Rodgers B (1978) Feeding in infancy and later ability and attainment: a longitudinal study. *Developmental Medicine and Child Neurology* **20**, 421–426.
Rogan WJ & Gladen BC (1993) Breast-feeding and cognitive development. *Early Human Development* **31**, 181–193.
Rush D (1984) The behavioral consequences of protein-energy deprivation and supplementation in early life: an epidemiological perspective. In *Human Nutrition. A Comprehensive Treatise*, pp. 119–154 [J Galler, editor]. New York and London: Plenum Press.
Simeon DT & Grantham McGregor SM (1990) Nutritional deficiencies and children's behaviour and mental development. *Nutrition Research Reviews* **3**, 1–24.
Taylor B & Wadsworth J (1984) Breast feeding and child development at five years. *Developmental Medicine and Child Neurology* **26**, 73–80.
Uauy R, Birch E, Birch D & Peirano P (1992) Visual and brain function measurements in studies of *n*-3 fatty acid requirements of infants. *Journal of Pediatrics* **120**, S168–S180.
Waber DP, Vuori-Christiansen L, Ortiz N, Clement JR, Christiansen NE, Mora JO, Reed RB & Herrera MG (1981) Nutritional supplementation, maternal education, and cognitive development of infants at risk of malnutrition. *American Journal of Clinical Nutrition* **34**, 807–813.
Walter T, de Andraca I, Chadud P & Perales CG (1989) Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics* **84**, 7–17.

Westwood M, Kramer MS, Munz D, Lovett JM & Watters GV (1983) Growth and development of full-term nonasphyxiated small-for-gestational-age newborns: Follow-up through adolescence. *Pediatrics* **71**, 376–382.

Winick M, Meyer KK & Harris RC (1975) Malnutrition and environmental enrichment by early adoption. *Science* **190**, 1173–1175.

https://doi.org/10.1017/S0029665100000069 Published online by Cambridge University Press