Effects of health and nutrition on cognitive and behavioural development in children in the first three years of life

Part 2: Infections and micronutrient deficiencies: Iodine, iron, and zinc

Sally M. Grantham-McGregor, Lia C. Fernald, and Kavita Sethuraman

Abstract

The following paper and its accompanying paper (Grantham-McGregor SM, et al. Effects of health and nutrition on cognitive and behavioural development in children in the first three years of life. Part 1: Low birthweight, breastfeeding, and protein-energy malnutrition. Food Nutr Bull 1999;20:53–75) review the literature on the conditions that are prevalent and considered to be likely to affect child development and are therefore of public health importance. The reviews are selective, and we have generally focused on recent work, particularly in areas that remain controversial. The reviews are restricted to nutritional and health insults that are important in the first three years of life. Where possible, we have discussed the better studies. This paper considers the effects of infections and the major micronutrient deficiencies: iodine, iron, and zinc.

Introduction

This review is restricted to early childhood infections that are common in low-income countries and are likely to affect children's development, thereby having public health implications. Repeated or chronic infections in pregnancy may lead to low-birthweight babies, and many specific infections, such as rubella, syphilis, and HIV, can have detrimental effects on the foetus. These issues are important but are not the focus of this paper and therefore they will not be discussed further.

Gastroenteritis, respiratory infections, and malaria are the most prevalent and serious conditions that may affect development in the first three years of life. It is estimated that children under five years of age in developing countries suffer from 3.5 episodes of diarrhoea per year and 4 to 9 respiratory tract infections in the first two years [1–3].

Other conditions have detrimental effects on children's development by affecting vision and hearing but are not life-threatening, such as repeated otitis media, which may impair hearing, and onchocerciasis, which causes blindness. Recently, there has been increased interest in the possible role of geohelminth infections in young children's development, which are estimated to affect greater than a quarter of the world's population [4]. However, infections are not usually intense in very young children, and school-aged children are at greater risk [5].

Mechanism

Infections are likely to affect children's development through several different mechanisms. Reduced dietary intake may occur secondary to anorexia or malabsorption, actual nutrient loss may occur secondary to protein-losing enteropathy, and increased demands may be present due to fever and the immune response. Anaemia and iron deficiency can also occur secondary to infection, haemolysis, and actual bleeding into the gut in the case of certain geohelminths. There is also the suggestion that the immune response itself may directly affect cognition and mood. In a series of studies in adults, Smith [6] showed that colds and influenza affect cognition and that even subclinical infection can impair performance. The impairments are present in the incubation period and for some time following recovery when symptoms are no longer present.

Infections also cause general malaise and apathy, and apathetic children generally demand and receive less stimulation from the adults in their environments. If a child suffers from long and repeated periods of decreased activity and exploration, this inactivity alone can lead to poor development. In Kenya, parents of children who suffer from frequent illness are less likely to interact socially with them but spend more time giving basic care [7].

The authors are affiliated with the Centre for International Child Health, Institute of Child Health, at the University College London Medical School in London.

It is important to remember that infections are more likely to occur in children from poor, overcrowded homes, with inadequate sanitation and water supply [8–10]. Furthermore, the symptoms are more likely to be prolonged where good medical care is unavailable. Children in these homes are already likely to be at risk of poor development from sociocultural deprivation. In addition, infections occur more often in children who are undernourished, another risk factor for poor development. It is likely that infections will have a greater effect on the development of children who are already vulnerable. Although there are ample reasons to suspect that infections would affect children's development, there are very few data on the topic, with the possible exception of the effects of parasites in older children.

Parasitic infections

There are several recent in-depth reviews of studies on the effect of parasitic infection on children's behavioural development [5, 11, 12], so we will discuss them only briefly here. *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and hookworm are all associated with poor levels of development in children as well as poor sociocultural and economic conditions. Therefore, randomized treatment trials are necessary to establish a causal relationship. The relationship of schistosomiasis to children's development and social background is even more difficult to understand, because often the more active, adventurous child is the one who becomes infected [13]. Thus, infected children may not always appear disadvantaged compared with peers [14].

Unfortunately, many studies have not had rigorous designs, and almost all concern older children. Two randomized controlled trials showed benefits to children's cognition following anthelminthic treatment. One concerned *T. trichiura* infections [15] and the other hookworm [16]. However, in the latter study iron treatment was also given, so that anthelminthic treatment cannot be separated from iron treatment. Other investigators failed to replicate these findings in children infected with *T. trichiura* or *Ascaris* in carefully designed studies [Watkins WE, personal communication, 1998; 11; 17; 18]. However, in post hoc analyses, subgroups of undernourished or heavily infected children showed some improvements with treatment. It is highly likely that extremely heavy infections that cause undernutrition or anaemia, such as *Trichuris* dysentery syndrome, will have a detrimental effect [19], but this level of intensity is less common. At present, it is an open question whether mild to moderate infections with geohelminths affect children's development in the absence of anaemia or undernutrition. One caution is that very young children are likely to be more vulnerable to infections, and where infections are prevalent in the first three years of life, we need to examine their effect.

The World Health Organization (WHO) estimates that 2,200 million of the world's population in some 90 countries are exposed to malaria [20]. Malaria is one of the most important causes of mortality and morbidity among young children, and it is estimated that 600,000 children under five years of age die of malaria annually [21]. Malaria affects children's growth [22, 23] and haemoglobin levels [24, 25]. Although it is likely that repeated attacks would detrimentally affect children's development, there is a surprising lack of data on the topic except for studies looking at the sequelae of cerebral malaria [26–28].

Diarrhoea and respiratory infections

Few studies have been conducted on the effects of diarrhoea and respiratory infections. In an exploratory longitudinal study of 164 infants in Taiwan, children who had episodes of respiratory infections or gastroenteritis in both the first and the second three months of life had lower scores on the Bayley motor (respiratory $p < .05$, gastroenteritis $p < .10$) and mental scales (both $p < .10$) at eight months of age [29]. When nutritional status was controlled, the trends remained and the effect of respiratory infections on the motor scale remained significant.

In an in-depth study of Kenyan toddlers, morbidity was recorded by weekly recalls from 18 to 30 months of age, behaviour was observed at home, the Bayley Test was administered at 30 months, and a comprehensive battery of cognitive and language tests was administered at five years of age. The toddlers were sick with mild to moderate infections an average of three days a week, with girls having more illness [7]. Girls with more illness played and vocalized less at home and had poorer cognitive skills than girls with less illness. This difference remained significant when extensive covariates and nutritional status were controlled for.

In a Jamaican study of stunted children, aged 9 to 24 months on enrolment, the number of days the children were too sick to play or run around in the following two years was related to their developmental levels on the Griffiths Test. This finding was probably an indicator of the more severe infections, as there was no relationship between the number of days with symptoms of respiratory infections and the number of days with diarrhoea.

In another study from Brazil [Morris S, personal communication, 1998], the number of days ill with diarrhoea in the first six months of life was related to poorer performance on the Bayley Test at 12 months of age in low-birthweight babies but not normal-birthweight babies. This later finding is another example of an interaction between two concurrent biological risk factors.

In conclusion, it appears that repeated infections in early childhood put the child at risk for poor psychomotor development. However, there are very few studies, and we were unable to find studies of long-term effects. It would be helpful to have more research on the topic, including countries with endemic malaria. From a policy perspective, it would appear that special attention should be paid to the development of children who suffer from repeated infections.

Iodine deficiency

According to the 1993 WHO report, 1.6 billion people live in areas of iodine deficiency, and approximately 20% of them have goitre. There are limitations in estimating prevalence using an indicator such as the total goitre rate, and more recent studies have begun reporting urinary iodine excretion. It is likely that the prevalence of iodine-deficiency disorders has fallen, as major efforts have been under way to iodize salt universally. Goals set by UNICEF and WHO to achieve universal salt iodization aim to have all salt for human and animal consumption iodized [30].

Most people at risk for iodine deficiency live in areas where the soils are low in iodine content due to leaching caused by high rainfall, melting snow, flooding, or glaciation. Mountainous areas are particularly at risk, with severely deficient areas in the Andes, the European Alps, the Himalayas, and mountain ranges in China. All crops grown in iodine-deficient soil are iodine deficient, which means that organisms that are dependent primarily on food grown in the earth will also experience iodine deficiency [31].

Iodine is a constituent of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are essential to human functioning because they influence skeletal maturation and the development of the central nervous system and regulate many other physiological processes [32–34]. Iodine deficiency in adults and children is usually characterized by low levels of T4 and high levels of thyroid-stimulating hormone (TSH) [35–39].

Iodine deficiency is the most common preventable cause of mental deficits and is a major public health issue [31, 40]. Iodine-deficiency disorders [41, 42] include a wide range of conditions, including increased pre- and postnatal mortality, goitre, and cretinism. The effects on development are now thought to include cognitive, sensory, and motor deficits. Iodine-deficiency disorders can also take their toll socio-economically, with lower work output per capita income and less productive farm animals in iodine-deficient areas [43].

Observational studies

Studies of goitrous and non-goitrous children

Studies have shown inconsistent differences between goitrous children and non-goitrous controls in terms of outcome measures of intelligence [44, 45]. The results may not be consistent because there is no clear relationship between the level of hypothyroidism and the presence of goitre [46].

Studies comparing children in iodine-deficient and iodine-sufficient areas

Consistent results have been obtained in studies evaluating the IQs of children living in severely or moderately iodine-deficient villages, as compared with children in iodine-sufficient or only mildly iodine-deficient areas (table 1) [47–56]. Children in areas of iodine deficiency have significantly lower levels of mental development when assessed with Raven's Matrices, cognitive tests, the Weschler Intelligence Scale for Children (WISC), Griffiths, or Bender-Gestalt Test [48–56]. In a meta-analysis of 18 studies evaluating the relationship between iodine levels in children and adults and cognitive function, individuals who had experienced some iodine deficiency had average IQs 13.5 points lower than controls [57]. Although the meta-analysis may be criticized for using such a wide range of study types, ages, and developmental outcome measures, it affirms the relationship between iodine deficiency and poor mental development. However, in most studies the complexity of factors that may affect both iodine intake and mental development of children was underestimated. Many confounding factors were not taken into account, such as socio-economic status, degree of isolation, access to health care, income levels, availability of water and electricity, quality of education, amount of inbreeding, and other cultural issues.

Another problem in evaluating neurodevelopmental outcome is that most studies used infant developmental assessments or IQ tests that may not have been culturally appropriate or standardized for the population. Furthermore, it is not possible from these studies to separate intrauterine effects of iodine deficiency from childhood effects.

Intervention studies

Maternal supplementation studies

Oral administration of oil to pregnant women pre-conception or during the first trimester has been shown to increase placental weight, reduce rates of prematurity, stillbirths, and abortions, and eliminate abnormal hormone levels in newborns [58, 59].

Several studies have investigated the effects of iodized oil given to women before and during pregnancy on their children's mental development (table 2) [60–69]. Early studies often used the weakest intervention design of comparing supplemented people in one village with non-supplemented people in another matched village. Based on the extensive investigations of children from two Ecuadorian villages, for example, iodi-

TABLE 1. Observational studies of children from iodine-deficient areas

Source	Study type and sample	Outcome measures	Results
Azizi et al. (1995) Iran [48]	*n* = 271, 6–16 yr, similar SES, education levels, schoolteachers, exposed to many of same influences (radio, TV, toys) 95 from A: 93% visible goitre, 39% low T4, 70% high TSH 103 from B: 66% visible goitre, 7% high TSH 73 from C: 22% visible goitre, normal thyroid function	Raven's IQ Bender-Gestalt ENT evaluation Endocrine evaluation	Raven's IQ: C > B* > A** (116 > 96 > 89) More errors when taking Bender-Gestalt Test in A & B than C** Hearing threshold lower in I-deficient group**
Tiwari et al. (1996) India [49]	*n* = 200, boys 9–15 yr, case-control design 100 children from 10 severely I-deficient villages: goitre >60%, cretinism 3.4%; cretins excluded from study 100 children from 4 mildly I-deficient control villages: goitre <10%, no cretinism Matched for SES, formal education level, age	Human maze learning Verbal learning rate Pictorial learning Achievement motivation scale	Children from I-deficient villages: lower scores in human maze learning**; slower verbal learning in serial learning** (not in free recall); worse performance in pictorial learning**; less motivation**; interaction between I deficiency & age
Azizi et al. (1993) Iran [50]	*n* = 105, 6–15 yr, children from 3 different villages 54 from Randan, area with hyperendemic goitre 20 from Zangoon, 2 mountainous regions with hyperendemic goitre 31 from Tehran, high goitre, normal thyroid function	Bender-Gestalt Test Hearing Thyroid function (T3, T4, etc.)	Thyroid function & somatic growth are normal Difference in IQ*** Tehran > Zangoon > Randan (117> 102 > 89) Many other differences in social background
Vermiglio et al. (1990) Italy [51]	*n* = 1089, 6–12 yr, living in 2 areas 368 from A, endemic cretinism 351 from B, no endemic cretinism 370 from C, no goitre or cretinism	Bender-Gestalt Test Neurological examination	Bender-Gestalt Test results of A & B v. C.*** (223 v. 27 performing defectively or borderline) More neuromuscular & neurosensory abnormalities in A & B***

continued on next page

nation was associated with a reduction in severe developmental defects such as cretinism and better scores on IQ tests [60, 61, 70, 71]. The study's design had many problems, including non-blinded treatment and inadequate matching of villages. Therefore, it is not possible to draw firm conclusions about the effects of supplementation on mental development from these data.

Using a more rigorous study design, Pretell et al. [62] compared the children of mothers from three iodine-deficient villages who were supplemented before conception with unsupplemented controls from the same villages. Although there were no significant differences between the groups in terms of their developmental quotient, the children of treated mothers scored higher

TABLE 1. Observational studies of children from iodine-deficient areas *(continued)*

Source	Study type and sample	Outcome measures	Results
Fenzi et al. (1990) Italy [52]	6–14 yr, living in 2 areas 384 from representative sampling of 1 area of moderate I deficiency, goitre prevalence of 52% 352 sex- & age-matched from control, I-sufficient area, with 5.6% goitre prevalence (some tests on subsample in class 3 & 5)	WISC-R Thyroid size Thyroid function Neuropsychological studies (in 50 children from each group) PM47	No overall difference in WISC or PM 47 In children from class 3: verbal IQ* (105 < 111); information* (9.5 < 12.1); vocabulary* * (11.1 < 13.9); coding* (8.3 < 10.3) No differences in children from class 5
Boyages et al. (1989) China [53]	*n* = 270, 7–14 yr, from urban & rural areas 141 born during iodized-salt prophylaxis in I-deficient rural village 51 from I-sufficient rural village 78 from I-sufficient urban populations (2 cities) Rural villages matched for several variables Urban areas not matched for any variables	Griffiths Mental Development Scales Hiskey-Nebraska Test of Learning Aptitude	Mean IQ lower*** in children from I-deficient village, in spite of iodized salt prophylaxis Treated rural: 72.4 Untreated rural: 84.4 Urban control 1: 108.6 Urban control 2: 106.3
Bleichrodt et al. (1987) Spain [54]	*n* = 355, 0–12 yr, from 7 different villages 162 from I-deficient area, goitre rate 66%, endemic cretinism 13% 193 from non-I-deficient area, goitre rate 13%, endemic cretinism 4% Matched for SES, degree of isolation, health care, education quality	Mental development: Bayley, McCarthy, Catell Motor development: Bayley, Oseretsky, Bender-Gestalt, fine motor	Lower scores of mental development in children from I-deficient areas for all age groups* More mentally retarded children in I-deficient group Infants: lower psychomotor score** Older group: lower manual dexterity & speed of reaction**
Bleichrodt et al. (1987) Indonesia [54]	*n* = 245, 6–20 yr, from 2 villages 106 from I-deficient village, goitre rate 68%, endemic cretinism 4.5% 139 from non-I-deficient area, goitre 3%, no endemic cretinism Matched for SES, degree of isolation, size	Test Intelligensi Anak & Test Intelligent Koletip, Indonesia Raven's Matrices Mental development (fluency, block design, vocabulary)	Lower scores of mental development in children from I-deficient area in all age groups* Differences in motor development after age 2.5 yr (eye-hand coordination, reaction time, balance)

continued on next page

at all ages. In a double-blind randomized trial in Zaire, the developmental quotients in infants from treated mothers were significantly higher than the developmental quotients in infants from non-treated mothers [63].

Perhaps the best and earliest longitudinal, double-blind, randomized, controlled trial was conducted in Papua New Guinea by Pharoah and Connolly and colleagues [65–69,72–75]. Intramuscular iodized oil was effective in preventing both types of endemic cretinism, and children whose mothers received iodized oil had better cognitive and fine motor skills than control children. Infant and childhood cumulative mortality

TABLE 1. Observational studies of children from iodine-deficient areas *(continued)*

Source	Study type and sample	Outcome measures	Results
Mehta et al. (1987) India [55]	$n = 60$, 6–16 yr, from 2 villages Both villages severely I deficient Children selected randomly from school, all goitrous; compared IQs of these children with those of normal rural Indian schoolchildren	WISC IQ Bhatia's Test Bender-Gestalt Test Goitre graded Urine samples Anthropometry Nutritional status	49 test children with IQ < 89, 11 with IQ ≥ 90 Children from test village scored worse** than normal schoolchildren on digit span, similarities, & Koh's Block Design
Querido et al. (1978) Indonesia [56]	$n = 245$, 6–20 yr 139 from village with 3% goitre rate 106 from village with 58% goitre rate Villages matched for employment, population, altitude	Motor development tests: pinboard, tapping, balance, reaction time, throwing balls, figure comparison	Treated children (6–8 yr) scored higher in pinboard **, tapping * Treated children (9–12 yr) scored higher in all tests** Treated adolescents (13–20 yr) scored higher in reaction time, tapping, figure comparison

*$p < .05$, **$p < .01$, ***$p < .001$.

Abbreviations: ENT, ear, nose, and throat; IQ, intelligence quotient; SES, socio-economic status; WISC, Weschler Intelligence Scale for Children.

Source: modified from ref. 47.

over the first 15 years of life was significantly reduced in the treated group. This study also showed links between maternal level of thyroid hormones and children's developmental outcomes.

The most recent maternal supplementation study, conducted in China [64], indicated that children born to women supplemented in the first and second trimesters had decreased prevalence of moderate or severe neurologic abnormalities, and increased developmental quotients compared with children whose mothers received iodine later in pregnancy.

All the studies discussed above indicate that maternal supplementation during gestation and the first trimester affects mental development in children. The studies from Papua New Guinea, China, and Zaire are sufficiently robust to establish that iodine deficiency in utero causes cretinism and poor development in childhood.

Childhood supplementation studies

A limited number of researchers have conducted iodine-supplementation trials in children (table 3) [76–80], but many of the studies had design flaws. The earliest supplementation trials evaluating developmental outcomes with children took place in Ecuador [77]. In these trials, 51 children aged 6 to 10 years from an iodine-deficient village were injected with iodized oil. Two years later, they were compared with children from a control village. The mean intelligence of the treated subjects was higher than that of the controls, but the results were significant only in the girls. In a Chinese study, children from an iodine-deficient area had significantly lower mean hearing thresholds, and the levels improved with treatment. However, no placebo group was measured at the same time [76]. A more recent treatment trial in Spain compared children from severely iodine-deficient areas who had been treated 32 months previously with children who had not been treated; no differences were found in scores on tests assessing manual dexterity and reaction speed [78]. Given the amount of time that elapsed between treatment and testing, it is likely that the effectiveness of the iodine supplement was reduced.

In a double-blind randomized controlled trial of schoolchildren in Bolivia, there were no improvements in any of the neurodevelopmental or IQ measures. However, the iodine status of the placebo group improved during the study, confusing the results [79]. In Malawi a double-blind placebo-controlled study in an area of endemic goitre found significant differences in the final test scores in three aggregate ratings on mental development that compared children who received iodine with those who received a placebo. However, there were no valid pre-test scores, so the findings are not conclusive [80].

The data from childhood supplementation studies

TABLE 2. Iodine intervention studies with mothers

Source	Sample	Intervention	Outcome measures	Results
Ramirez et al. (1969) Ecuador [60]	Two I-deficient villages: pregnant women in 1 treated not in the other. Group I: children of mothers treated during mo 4–7 of pregnancy Group II: children of mothers treated before conception Controls: children of untreated mothers	Mothers treated with iodized oil (regular doses to maintain urinary excretion of 50 µg/g creatinine until 4–5 yr after 1st injection) Iodized salt available in area for 1 yr before treatment	Stanford-Binet	Difference between group II & controls ($p < .002$) No differences between group I & controls
Ramirez et al. (1972) Ecuador [61]	Group I: children of mothers who received I before 6th mo of pregnancy Group II: children of untreated mothers	Same as above	Gesell	Higher % of children <4 yr old in village receiving iodized oil performed in normal range of IQ scores than children in control village
Pretell et al. (1972) Peru [62]	$n = 456$ newborns 56% iodized group 44% placebo, I-deficient	Mothers received dose of I during pregnancy & another dose 3 yr later	Stanford-Binet Brunet-Lezine Physical examination Urinary I	No significant differences, but scores higher in iodized group
Thilly et al. (1980) Zaire [63]	Double-blind randomized trial in area of severe I deficiency All children assessed at 4–25 mo $n = 115$ treated at average 28th wk of pregnancy $n = 104$ placebo	500 mg iodized oil, or I-free vitamins 1 treatment	Brunet-Lezine scale (DQ) Thyroid function	In children whose mothers were treated: higher DQ (115> 104**), lower infant mortality rate*, higher maternal I concentration**
Cao et al. (1994) China [64]	All children 2 yr $n = 120$ infants whose mothers were treated during 1st or 2nd trimester $n = 752$ whose mothers were treated in 3rd trimester	400 mg iodinated oil Treated again at 6 mo or annual reevaluations	Bayley Scales (DQ) Anthropometry	In children whose mothers were treated earlier: higher DQ (90 > 75***), decreased prevalence of moderate or severe neurological abnormalities (2% v. 9%**), decreased prevalence of microcephaly (11% v. 27%**)
Pharoah et al. (1971) Papua New Guinea [65]	Families in 16 villages randomly assigned to treatment or placebo 498 births to treated mothers 534 births to untreated mothers	Same as above	Incidence of cretinism, maternal T3 & T4 levels	Higher number of cretins born to unsupplemented mothers

continued on next page

TABLE 2. Iodine intervention studies with mothers *(continued)*

Source	Sample	Intervention	Outcome measures	Results
Connolly & Pharoah (1979) Papua New Guinea [66]	Children from 5 of above villages 115 births to treated mothers 79 births to untreated mothers	Same as above	Same as above & manual dexterity (bead threading, pegboard)	Better values in treated group for pegboard*, bead threading**
Pharoah et al. (1981) Papua New Guinea [67]	Same 5 villages Children aged 6–11 yr of women who had thyroid function measured $n = 37$ or 35 for some tests	Same as above	Same as above	Significant correlations between motor ability of child & maternal T4 level
Pharoah et al. (1984) Papua New Guinea [68]	Same 5 villages $n = 20$ children aged 10–12 yr whose mothers had thyroid function measured in pregnancy	Same as above	Same as above & Pacific Design Construction Test	Significant correlations between both intellectual & motor ability of child & maternal T4 level
Connolly et al. (1989) Papua New Guinea [69]	Same 5 villages $n = 44$ children aged 14–16 yr whose mothers had thyroid function measured during pregnancy	Same as above	Motor performance, card sorting	Significant correlations between all mental & motor scores & maternal T4 level

*$p < .05$, **$p < .01$, ***$p < .001$.

Abbreviations: DQ, developmental quotient; IQ, intelligence quotient.

Source: modified from ref. 47.

are less clear than those from maternal supplementation studies, probably because there are only a few studies and only one had a randomized design with pre- and post-treatment measures.

Conclusions about iodine deficiency and development

A substantial number of studies have examined iodine deficiency and its effect on child development. However, many of them have design problems. In spite of these problems, it is possible to conclude that supplementation is critically important pre-conception and in the first two trimesters of pregnancy for women who live in iodine-deficient areas. Few studies have looked at the effects of supplementation on children's cognitive function and school achievement, and the findings are inconsistent. However, supplementation for school-aged children in iodine-deficient areas remains important in order to reduce the incidence of goitre. Within supplementation programmes, girls should be targeted if possible because of the risk of pregnancy.

Policy implications

Clearly, iodine deficiency is a public health problem of global concern, and universal salt iodization is a priority [81]. Fortification of all salt for human and animal consumption is the easiest and most cost-effective method of iodization. However, the voluntary intake of salt is not always enough to protect the population from iodine deficiency. In Germany, for example, iodization of salt and of pig and cattle food was mandatory only in East Berlin. As a consequence, infants born in West Berlin were more likely to be iodine deficient, despite the availability of iodized salt [82]. Many factors hinder the progress of universal salt fortification, including poor storage, insufficient market control, insufficient monitoring, inattention to cost, limited programme integration, and governmental complacency [43]. Thus, the approach to salt iodization must be tailored to each particular country's needs.

Although salt is the most desirable option, other possible forms of fortification do exist. According to WHO [83], iodized oil should be used in situations in

TABLE 3. Iodine intervention studies with children

Source	Sample	Intervention	Outcome measures	Results
Wang & Yan (1985) China [76]	*n* = 150, 7–11 yr 120 from areas of severe I deficiency (30 from 4 different villages) 30 from non-endemic areas Excluded children with poor scholastic record, goitre or hearing impairment in all villages, similar SES, except for control	I prophylaxis for 3 yr	Mean hearing threshold Hearing at different frequencies	Lower hearing threshold in untreated groups*** improved with treatment
Dodge et al. (1969) Ecuador [77]	Children from 1 village (*n* = 51) aged 6–10 yr injected compared after 2 yr with those in control village	2 ml iodized oil	Goddard Test Goodenough, draw-a-man	Mean intelligence of treated > controls, girls***
Bleichrodt et al. (1989) Spain [78]	*n* = 287, 6–12 yr from several different villages 103 children from I-deficient areas who had been treated 32 mo earlier 102 children from I-deficient areas 82 control children from non-I-deficient areas Areas matched for SES, degree of isolation, health care, quality of education	Single oral dose (2 ml) of Lipiodol	Manual dexterity Reaction time	No difference in mean values or distribution curves
Bautista et al. (1982) Bolivia [79]	*n* = 200, 5.5–12 yr Double-blind assessment 100 girls, 100 boys randomly assigned to treatment or placebo	Oral dose of 1.0 ml iodized poppyseed (Ethiodol) 475 mg I control received 1.0 ml uniodized oil 1 treatment	Bender-Gestalt School grades Thyroid size Stanford-Binet (IQ) Urinary I	IQ showed significant* dependency on goitre size change in both groups (especially in girls)
Shrestha (1994) Malawi [80]	*n* = 134, 6–8 yr from same area of endemic goitre Double-blind placebo-controlled study 72 children received I 72 children received placebo	Single oral dose (1 ml) of iodized oil	Fluid intelligence Crystallized intelligence Perceptual skill	Fluid intelligence*** Crystallized intelligence* Perceptual skill***

Abbreviations: IQ, intelligence quotient; SES, socio-economic status.

which the prevalence of iodine-deficiency disorders is moderate or severe, cretinism and neonatal hypothyroidism are present, or universal salt iodization programmes would not reach women of reproductive age in one to two years. Although it is certain that women of reproductive age should be given iodine at all costs, it is not yet clear if schoolchildren should also be given priority. Single oral doses of Lipiodol, 240 mg for 6 months or 480 mg for 12 months, have been shown to prevent the worst iodine-deficiency disorders, such as hypothyroidism and cretinism, and doses much higher than 400 mg are usually not recommended [59, 84–87].

Eighty-eight of the 97 developing countries iodize salt. However, problems with the marketing and production of adequately iodized salt still prevail. Several countries face the challenge of achieving universal salt iodization by assisting and encouraging many small producers to iodize salt. The next step towards the successful achievement of universal salt iodization will require ongoing monitoring of salt iodization through its various stages of production and distribution, including monitoring urinary iodine excretion.

Iron deficiency

In 1985, the estimated prevalence of anaemia (haemoglobin <110 g/L) in children under five years of age was 46% to 51% in developing countries and 7% to 12% in developed countries [88]. It is difficult to be certain of current prevalence levels, because the Opportunities for Micronutrient Interventions (OMNI) still cite a 51% prevalence in young children [89]. Anaemia has many different causes, but by far the most common is iron deficiency. Therefore, it is reasonable to assume that most anaemic children are iron deficient. Anaemia is most prevalent in children between 6 and 24 months of age, and the major causes are inadequate dietary intake of bioavailable iron, malaria, and parasitic infections.

In adults, iron deficiency affects work capacity and work productivity [90]. In one study, anaemic Indian children five to six years of age had lower work capacity than non-anaemic children [91]. For some years there has been concern that iron deficiency affects children's cognitive, motor, and behavioural development, and a substantial number of studies have been conducted to investigate this. Unfortunately, many of the studies have failed to use a randomized design.

Iron-deficiency anaemia and concurrent development

It is well established that iron-deficient anaemic children usually have poorer levels of development than non-anaemic children. Many correlational studies have linked iron status with current development [92–96]. Associations have been found between iron-deficiency anaemia and poor concurrent development in pre-intervention measures of infants who were subjects in treatment trials. Infants with iron-deficiency anaemia scored lower on the Bayley Test of Mental Development in Indonesia [97], Guatemala [98], Chile [99], and Costa Rica [100, 101] and on the Bayley Test of Motor Development [97, 98, 100, 101]. Only a few studies have failed to find associations with iron-deficiency anaemia and development [102, 103].

Lozoff examined the level of anaemia that was associated with a decline in development and found that infants with haemoglobin below 150 g/L had significantly lower motor development scores than infants with higher haemoglobin levels, whereas infants with haemoglobin levels below 100 g/L had lower mental and motor development scores [100]. Walter and colleagues reported that infants who had anaemia for long periods of time had poorer development than those who had anaemia for only a short period [104].

Longitudinal studies of development of children who had iron-deficiency anaemia in infancy

Not only is anaemia associated with concurrent poor development, but in several studies it has also been shown to predict future poor development. In a longitudinal study of growth and development of children in the first two years of life in Yugoslavia [105], children's haemoglobin level at 18 months predicted their developmental levels at 24 months.

In five longer-term studies (table 4) [106–109; Hurtado E, personal communication 1998], children who were anaemic in infancy continued to have poor levels of mental development several years later, even when their iron deficiency had been treated successfully [106–108, 110]. Costa Rican children who were anaemic between 12 and 23 months of age and were treated successfully with iron were followed up at five years of age and given a comprehensive battery of tests. Those who had been anaemic were normal in all measures of nutritional status, but they scored lower than control children on most of the cognitive and motor tests. They also came from less stimulating homes, but after a large number of confounding variables had been controlled for, the formerly anaemic children still scored lower than the controls on tests of visual motor integration, gross and fine motor skills, and subtests of the Woodcock-Johnson pre-school battery and performance IQ [106].

In a similar study in Chile, five-year-olds who were anaemic at 12 months and had been treated scored worse on a test battery including fine motor proficiency, psycholinguistic ability, and pre-school abilities [104, 107, 111].

In a third longitudinal study, middle-class Israeli children had their haemoglobin levels examined at 9 to 10 months of age, and their developmental levels or IQs were assessed at 2, 3, and 5 years of age. Children

TABLE 4. Longitudinal studies of infants with iron-deficiency anaemia

Study	Sample	Measurements	Results
Lozoff et al. (1991) Costa Rica [106]	163 of 191 lower-middle-class children from a study between 12 & 24 mo of age retested at 5–6 yr Group 1: 30 with Hb ≤100 g/L in 1st study Group 2: 133 children with ≥100 g/L	Battery of tests: WPPSI, Bruininks-Oseretsky motor test, Woodcock-Johnson psychoeducational battery, VMI, Goodenough draw-a-man, neurological examination	After several confounding variables had been controlled for, group 1 had significantly lower scores in WPPSI performance scales, gross & fine motor skills, VMI, psychoeducational battery
De Andraca et al. (1990) Chile [107]	Lower- & middle-class participants in a previous study of Fe fortification from 3 to 12 mo; from an original 196 chose 41 formerly anaemic & 29 non-anaemic	Battery of tests: Stanford-Binet, Illinois psycholinguistic abilities test, psychoeducational battery, Bruininks-Oseretsky motor test, VMI, neurological examination	Anaemic group had significantly lower scores in all tests except tests of gross motor ability & more neurological immaturity
E. Hurtado et al. (1998) USA [personal communication]	3,322 participants in the WIC programme, Florida Hb measured on enrolment	School records at age 10 (5th grade)	Hb ≤ 90 g/L had small increased risk of learning disability, after many confounders had been controlled for
Palti et al. (1985) Israel [108]	Middle-class children had Hb screened at 9 mo *n* = 873 at 2 yr *n* = 388 at 3 yr *n* = 239 at 5 yr	2 yr Brunet-Lezine 3 yr 5 yr WPPSI IQ	Anaemic children had significantly lower scores at 2, 3, & 5 yr After maternal education & birthweight had been controlled for, significantly lower only at 5 yr
Palti et al. (1985) Israel [108]	Same study as above 20 children with Hb ≤ 105 g/L 56 controls > 115 g/L	2nd grade children teacher rating behaviour & school achievement	Anaemic children had significantly lower school achievement & behaviour rating after confounders had been controlled for
Cantwell (1974) USA [109]	61 infants studied from birth to 7 yr 32 infants became anaemic (Hb < 100 g/L) 29 received Fe & were not anaemic Assignment method not given	Neurological examination at 6–7 yr Stanford-Binet	Anaemic children's IQ = 92 Non-anaemic children's IQ = 98 (no statistics given) More neurological soft signs in anaemic children

Abbreviations: Hb, haemoglobin; IQ, intelligence quotient; VMI, visual motor integration; WPPSI, Weschler Pre-school & Primary Scale of Intelligence.

who had haemoglobin < 100 g/L scored lower than control children at each age level. However, when maternal education and birthweight were controlled, the difference was only significant at five years [110]. These children were examined again in the second grade [108], when the formerly anaemic children had poorer school achievement ratings than children who had haemoglobin levels above 115 g/L. The authors pointed out that maternal education made a much larger contribution to the ratings than a history of anaemia.

In a study published only in abstract, Cantwell reported an increased incidence of neurological delay in seven-year-old children who were anaemic in infancy [109].

Hurtado and colleagues (personal communication, 1998) took an epidemiological approach to the problem. They used records from Dade County, Florida, of birthweight, enrolment in WIC programmes (a national programme of nutritional supplementation), and achievement in elementary school. Based on the 3,771 records with complete data, 10-year-old children who had been anaemic on enrolment in the WIC programme in the first four years of life were more likely to be receiving special education. This finding remained after several variables had been controlled for (birthweight, ethnicity, maternal education, etc.).

Conclusions from longitudinal studies

The depressing implication of these studies is that iron-deficiency anaemia leads to irreversible changes to children's development. However, as with most other nutritional deficiencies, iron deficiency is associated with many environmental disadvantages [106, 112], which themselves may detrimentally affect children's development. Most of the studies discussed above attempted to control statistically for social factors that could contribute to the differences between groups, such as home stimulation and maternal IQ and education. It could still be possible that differences in home environments accounted for the differences between the two groups. Some measures of the environment may not have been sensitive, or there may have been other unmeasured variables that influenced children's development. Thus, to demonstrate a causal relationship, randomized controlled trials are essential.

Treatment trials in children under two years of age

Short-term treatment trials

The first treatment trials were short, usually lasting less than two months, and produced no convincing evidence of benefit to children's developmental levels. Children who received short-term treatment showed improvements in scores on the Bayley Test of Mental Development [99], although there were no placebo anaemic groups, so that test practice could have accounted for the improvement. Four short-term treatment trials with placebo groups in the United States [113], Guatemala [98], Costa Rica [100], and Chile [104] failed to find significant treatment effects, although the sample sizes were extremely small in most of the studies.

Treatment trials longer than two months

Studies with longer-term supplementation for two to six months yielded inconsistent although more positive results (table 5) [97, 100, 101, 104, 114]. Unfortunately, few of them had randomized designs. Three studies had no placebo group, and all anaemic children were treated and compared with non-anaemic children. In two of the studies, anaemic children were treated for three months [100, 104], and in the other they were treated for six months [101]. In these three studies, the anaemic children initially had lower scores on the Bayley mental scales than the non-anaemic children, and in two of the studies they had lower scores on the motor scale as well [100, 104]. The treated anaemic children did not improve more than the non-anaemic ones in either scale in any of the studies. In one study [100], the group of children achieving complete haematological normality significantly improved relative to the non-anaemic group. However, Walter and colleagues [104] found no improvement with supplementation in a similar subgroup.

Randomized controlled trials

Only two of the treatment trials were randomized. In England 97 anaemic children were randomly assigned to a vitamin C and iron supplement or vitamin C alone. There were no significant differences on the Denver Mental Development Test after two months of treatment. However, more iron-treated children than placebo-treated children had a normal rate of development. Also, the Denver Test was not designed to be sensitive to small differences, which may account for the failure to find an effect.

In the second randomized control trial, 50 anaemic children aged 12 to 18 months were assigned to iron treatment or placebo. The treated group showed a dramatic overall improvement in both mental test scores (18.8 points higher in the treated group than in the placebo group) and motor test scores (18.4 points higher in the treated group than in the placebo group) after four months of treatment (fig. 1) [97].

Conclusions from treatment trials

When assessing the results of treatment trials of children of this age, there is no consistent evidence that short-term treatment improves development. The three longer-term trials, which had no anaemic placebo group [100, 101, 104], as well as the longitudinal studies discussed previously, all suggest that treatment does not improve development in anaemic children. The failure of six months of treatment to produce even a hint of reduction of the deficit in anaemic children in the Costa Rican study [101] is particularly worrisome. However, without a placebo group, we do not know how untreated anaemic children would have developed, and we cannot assume that they would develop at the same pace as non-anaemic children. Therefore, the study design prohibits making any firm conclusions.

The Indonesian study [97] stands alone in having a randomized design and showing a large treatment effect in anaemic infants following longer-term treatment. The design was robust, but the study had only 25 treated

TABLE 5. Trials of iron treatment given to anaemic children under two years of age for at least two months

Study	Sample	Treatment	Test	Results
Aukett et al. (1986) UK [114]	*n* = 97 IDA 17–19 mo Random assignment to treatment or placebo	Fe & vitamin C for 2 mo; placebo was vitamin C	Denver Test	No significant treatment effect on Denver scores; significantly more treated children achieved normal rate of development
Lozoff et al. (1987) Costa Rica [100]	1) 12–24 mo, *n* = 52 IDA, *n* = 35 non-IDA Random assignment to treatment or placebo 2) Children from group 1 after the 1-wk Bayley Test; all IDA group treated, non-IDA group given placebo	Oral or intramuscular Fe for 1 wk	Oral Fe for 12 wk	Bayley Test Initially anaemic group had lower MDI & PDI scores; no treatment effect after 7 days IDA children who had complete Fe status recovery after 3 mo, not significantly different from non-anaemic MDI & PDI at 15 mo; anaemic group with partial recovery still had significantly lower scores
Walter et al. (1989) Chile [104]	1) *n* = 196, 3 mo stratified by BF, randomly assigned to treatment or placebo; no baseline measures 2) *n* = 39 IDA, *n* = 30 not IDA, from pooled group at 12 mo randomly assigned to treatment or placebo 3) All children from group 2 given Fe treatment	1) Fe-fortified food from 3 to 12 mo; tested at 12 mo 2) Oral Fe for 10 days 3) Oral Fe for 3 mo	Bayley Test	1) Groups pooled, anaemic children had lower MDI & PDI at 12 mo 2) No treatment effect on MDI or PDI 3) No difference in change in MDI or PDI between anaemic & control groups
Idjradinata & Pollitt (1993) Indonesia [97]	12–18 mo 50 anaemic (IDA) 29 non-anaemic Fe-deficient 47 Fe-sufficient Each randomly assigned to treatment or placebo	4 mo Fe treatment	Bayley Test	Initially IDA significantly lower MDI & PDI than other 2 groups, IDA significantly improved & caught up to the other 2 groups
Lozoff et al. (1996) Costa Rica [101]	12–23 mo *n* = 32 IDA *n* = 54 non-IDA All IDA treated & non-anaemic randomly assigned to treatment or placebo	6 mo Fe treatment	Bayley Test	IDA significantly lower MDI on enrolment & showed no improvement, PDI lower (non-significant) & remained so throughout

Abbreviations: BF, breastfeeding; IDA, iron-deficiency anaemia; MDI, mental development index of the Bayley Test; NS, not significant; PDI, psychomotor development index of the Bayley Test.

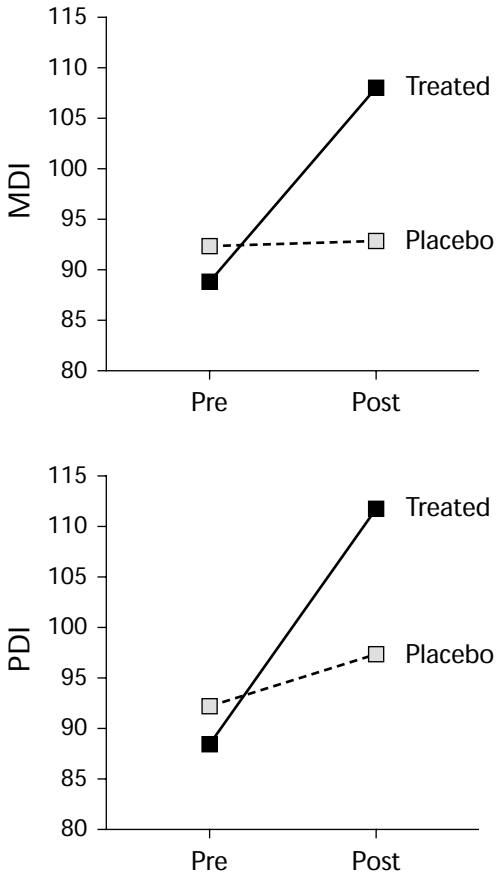

FIG. 1. Graphs of (a) mental (MDI) and (b) psychomotor (PDI) development in treated and placebo iron-deficient anaemic children [97]

children and clearly needs replicating before it can be extrapolated to all populations.

Prophylactic treatment trials

Six prophylactic randomized controlled trials (table 6) [Williams J, personal communication, 1998; 104; 115–118] involved giving iron supplementation in the first year, usually before any degree of anaemia developed. Their aim was to prevent anaemia from developing in one group of children. Two recent large studies, one in England [118] and the other in Chile [117], reported no difference in development between the treated and placebo groups at the end of the supplementation period. In the Chilean study, 944 non-anaemic six-month-old children were randomly assigned to iron supplementation or placebo; the children were tested on the Bayley Test at 12 months of age. In the English study, 9-month-old children were enrolled and supplemented until they were 18 months old, when no difference was found on the Bayley Test between supplemented and non-supplemented children. These two studies were published only in abstract form, so the full details cannot yet be evaluated.

Two other studies are difficult to interpret [104, 115]. In a randomized trial in Papua New Guinea, two-month-old children were given intramuscular iron or a placebo [115]. At 12 months they were given tests of habituation. Unfortunately, the high prevalence of malaria parasitaemia confused the results, and there was no clear treatment effect. Those children without parasitaemia and treated with iron had longer fixation times than the children receiving placebo, indicating better attentional abilities; habituation was not affected. In another randomized trial [104], children were given fortified formula or food from three months of age. We were unable to find results reported by the original randomization groups, because the anaemic children from both groups were pooled and said to have lower scores than non-anaemic children.

Two studies showed clear benefits from iron prophylaxis. In a Canadian study [116], 283 infants between birth and two months of age, mostly from poor Amerindian families, were randomly assigned to iron-fortified formula or regular formula. The difference in the incidence of anaemia between the two groups reached a maximum of 19.9% (28.0 vs 8.1) at six months of age and declined to 7.8% at 15 months. The motor scores of the iron-fortified group on the Bayley Test were not different at 6 months but were significantly higher at 9 and 12 months of age (maximum difference, 1/2 standard score). However, the benefit was transient and no longer significant at 15 months. There was no treatment effect on the mental scale. Although this was a well-designed study, the loss of 129 children by 15 months raises doubt as to the validity of the findings at this age.

A second important study was recently reported from England [Williams J, personal communication, 1998]. One hundred poor inner-city children were randomly assigned at 7 months of age to iron-fortified formula or unfortified cow's milk until 18 months of age. On enrolment, some children were already anaemic (16% in the non-supplemented and 13% in the supplemented group). By 12 months the proportions were 31% and 3%, and by 18 months they were 33% and 2%, respectively. The groups had similar scores on the Griffiths Test on enrolment at 18 months, but at 24 months their developmental quotients and scores in every subscale except the locomotor were significantly higher than those of the group receiving cow's milk (fig. 2). The latter group showed a marked decline in scores between 18 and 24 months of age, which did not occur in the fortified group. A decline around this age is well established in deprived children. The main problem with this study is that the ingredients of formula differed from cow's milk in several ways other than the iron content, and these other ingredients may have played

TABLE 6. Prophylactic iron treatment trials in infancy (in chronological order)

Study	Sample	Treatment	Test	Results
Heywood et al. (1989) Papua New Guinea [115]	*n* = 96, 2 mo Longitudinal cohort Matched sex & BW Random assignment to treatment or placebo All checked for malaria parasites	Injection of Fe or placebo at 2 mo	12 mo: habituation test, examination for malaria parasites	Malaria confused the results; in parasite-free children only, treated children had higher fixation times No effect on habituation
Walter et al. (1989) Chile [104]	*n* = 196, 3 mo Stratified by BF Randomly assigned to treatment or placebo	Fe-fortified or non-fortified food from 3 to 12 mo	12 mo: Bayley, no baseline measures	No significant benefit on Bayley scores Anaemic children in pooled groups had lower MDI & PDI scores
Moffatt & Longstaffe (1994) Canada [116]	*n* = 283, 6 mo Bottle-fed infants, randomly assigned to treatment or placebo at birth (*n* = 154 at 15 mo)	Fe-fortified or regular formula	6, 9, 12, 15 mo: Bayley	PDI not significantly different at 6 & 15 mo, significantly better in Fe-treated group at 9 & 12 mo MDI not different
Lozoff (1996) Chile (abstract only) [117]	*n* = 944, 6 mo Randomly assigned to treatment or control	Fe or no Fe, 6–12 mo	12 mo: Bayley	No treatment effect on Bayley scores 4% IDA in control group, 15% in treated
Williams et al. (1998) England [personal communication]	*n* = 100 inner-city infants on cow's milk Randomly assigned to treatment or control at 7 mo	Fe-fortified formula or cow's milk from 7 to 18 mo	7, 18, 24 mo: Griffiths	18 mo: no treatment effect 24 mo: significant treatment effect on DQ & all subscales except locomotor

Abbreviations: BW, birthweight; DQ, developmental quotient; IDA, iron-deficiency anaemia; MDI, mental development index of the Bayley Test; PDI, psychomotor development index of the Bayley Test.

a role. This study illustrates the importance of conducting longitudinal studies when concerned with child development outcomes, because if the study had stopped at 18 months when the supplement was stopped, no effect would have been evident. It is possible that the developmental deficit takes time to develop, which may explain the failure of other preventive trials to show a benefit [101, 118].

Conclusions from preventive trials

It appears that preventive trials benefit some populations. The two later studies were both randomized controlled trials, although one had a large loss and the other did not give only iron. The difference in proportion of anaemic children between the groups in the English trial [Williams J, personal communication, 1998] was considerable (30%), and the follow-up continued for 17 months, which may explain why benefits were found. In contrast, in most of the other studies, the duration was shorter and the difference between the groups in anaemia was not so great.

Iron-supplementation studies of anaemic school-aged children

Studies with schoolchildren will not be discussed in detail, since our focus is on younger children. However, when interpreting findings from studies in younger children, it is useful to be cognizant of findings from

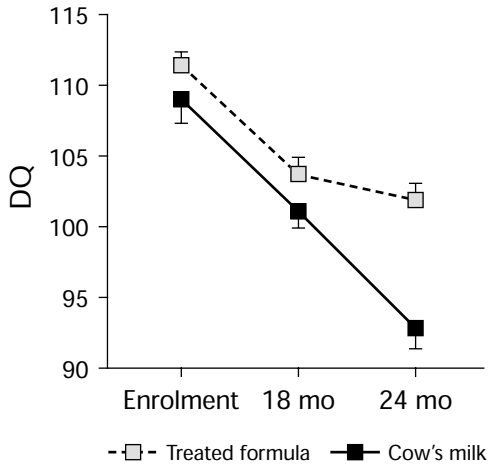

FIG. 2. Griffiths developmental quotients of children given iron-fortified formula (n = 50) or unmodified cow's milk (n = 50) [Williams J, personal communication, 1998]

older children. Unlike studies in the first two years of life, studies in older children have had reasonably consistent results. Benefits to children's performance on tests of cognitive function or school achievement were reported in India [119], Indonesia [120–122], and Egypt [123]. It is unclear why one well-designed study in Thailand failed to find an improvement in school achievement when anaemic children were given iron [124].

Mechanisms

Lozoff reviewed the possible mechanisms whereby iron deficiency might affect behaviour and mental development [125]. Research in animals suggested that the brain is directly affected. Total brain iron is reduced in iron deficiency, and if it occurs early in life, there is a permanent reduction despite correction of anaemia [126, 127]. Iron is essential for myelination, and iron-deficient rats show hypomyelination. In addition iron plays a role in neurotransmitter function, and dopamine function is decreased [126–128].

Another possible mechanism is through the children's behaviour itself, which could lead to poor development. Anaemic children have been reported to be inhibited [129], and recently systematic observations showed that they stay nearer their mothers, are wary and hesitant, and interact less with family members [125, 130]. This behaviour is similar to that of malnourished children [131]. It has been hypothesized that the children are isolated from their environments and thus fail to explore and acquire skills at a normal rate, a phenomenon known as "functional isolation" [132].

Recent work in children may explain the link between central nervous system changes and behaviour [125]. Infants with iron-deficiency anaemia had prolonged latency in auditory brain stem responses, which remained after correction, providing evidence that the central nervous system is affected in iron-deficiency anaemia. Iron-deficient infants also have reduced vagal tone, which remains after correction of iron deficiency. Reduced vagal tone has been linked to behaviour changes, including poorer developmental outcome, extreme inhibition, and reduced ability to cope with stress [133, 134]. These changes could explain some of the behaviours of iron-deficient children.

Summary of findings and conclusions on iron deficiency and child development

Association between iron-deficiency anaemia and development

The association between iron-deficiency anaemia in the first two years and concurrent and future poor developmental levels is well established. It is also well established that iron-deficiency anaemia is associated with many sociocultural disadvantages.

Iron-deficiency anaemia causes poor development

School-aged anaemic children benefit from iron treatment in terms of cognition and school achievement, indicating that there is likely to be a causal association between iron treatment and improved cognition. It is extremely unlikely that older children are more sensitive to iron-deficiency anaemia than younger children.

There is evidence from two preventive randomized controlled trials that iron deficiency detrimentally affects child development [116; Williams J, personal communication, 1998], although the benefit is transient in one study. However, as two recent trials failed to find a benefit [101, 118], we need to carefully examine the data when they become available in order to determine why these studies have inconsistent findings. Possible reasons are the duration of the treatment, the age of the child at testing, and the difference in the prevalence of anaemia between the treated and the placebo groups. No trials have been reported in countries with extremely high levels of anaemia. No consistent evidence suggests that mental development is affected differently from motor development.

Response of children with iron-deficiency anaemia to treatment

Short-term treatment does not benefit children's development during the period of treatment. In children under two years of age, the evidence for an improvement in development in response to longer-term treatment of iron-deficiency anaemia rests on one small randomized trial [97], and these findings need to be replicated. Several studies failed to show an improvement with treatment, but they had less robust designs.

Policy implications

Many developed countries have reduced pre-school anaemia through the use of iron-fortified formula, complementary foods, and iron supplements. For example, in the United States the prevalence of anaemia has seen a steady decline of 5% among low-income children who received iron-fortified foods through the federal food supplement programme for women, infants, and children [135]. However, among similar low-income populations in Canada and Britain, the prevalence of iron-deficiency anaemia among low-income children remains around 25% or even higher [136].

At the 1990 World Summit for Children, goals were set to reduce iron-deficiency anaemia by a third of the 1990 levels by the year 2000 [20]. However, large-scale interventions in developing countries to reduce anaemia have had little success; most approaches have been limited to providing supplements [137]. Although governments have adopted policies to reduce iron-deficiency anaemia among pregnant women and pre-school children, often these are not enforced or implemented. Recent research has demonstrated that approaches such as the control of malaria and other parasitic infections, long-term supplementation, and food fortification can successfully reduce the prevalence of iron-deficiency anaemia [138, 139]. These approaches need to be considered by policy makers and governments as possible means to reduce the prevalence of iron-deficiency anaemia. Furthermore, anaemic children usually have other risk factors for poor development; if these children are to attain optimal development, an integrated approach, which includes child-development activities, is needed.

Zinc deficiency

Zinc deficiency is now recognized as a public health problem [140]. Zinc deficiency is associated with complications of pregnancy and birth outcomes [141], impaired immune function [142], and increased duration and severity of diarrhoea in children [143]. It also causes growth retardation, and several studies have shown that zinc supplementation can produce a significant growth response in height and weight-for-height [144–146].

Zinc deficiency occurs in many countries, but the actual number of people affected is unknown because of difficulties in diagnosis. The quality of the diet, the incidence of infection, and the physiological stage of development all determine the prevalence of zinc deficiency. It is common where diets contain little meat and high levels of phytate or fibre, which reduce zinc bioavailability. These characteristics are common in the diets of many developing countries. Cow's milk also inhibits zinc bioavailability, whereas breastmilk does not. In addition, competitive interactions between zinc and copper and between zinc and iron may further limit availability [147].

Requirements for zinc are increased during periods of rapid growth, such as infancy and pregnancy, and in addition, increased loss in the stool occurs in diarrhoea. Zinc deficiency is therefore likely to be common in young undernourished children who have frequent diarrhoea.

There is concern that zinc deficiency may detrimentally affect children's mental development and behaviour. Several studies in primates have shown that zinc deficiency affects behaviour [148]. A few studies conducted in children are summarized in table 7 [143, 147, 149–152]. Children's behaviour in their homes was the outcome of interest in two randomized, controlled trials of zinc supplementation. In a study of Indian children aged 12 to 24 months, their activity was divided into five groups according to intensity, and the supplemented group spent more time in the highest-intensity category; ratings of their overall activity level were also significantly increased [143]. In a study in Guatemala [150], the supplemented children were observed to sit and play more often and lie down less often than unsupplemented children. However, the definition of play was unclear, and no difference in the age of attainment of motor milestones was found. Neither study analyzed the results by change in scores.

One study examined the effect of supplementation on infant's psychomotor development. In a randomized trial of 52 very-low-birthweight children in Canada [152], the group that received zinc and copper supplements had significantly higher scores on the locomotor subscale of the Griffiths Test than the unsupplemented group after approximately six months. The other subscales were not affected.

In two randomized, controlled trials of the effects of zinc supplementation on the cognitive function of schoolchildren, no differences were found. However, an extremely limited range of cognitive functions were tested [147, 151]. In a recent Chinese study [149], schoolchildren showed benefits to their scores on a wide range of cognitive tests after 10 weeks of zinc supplementation as compared with a group receiving a micronutrient mixture. The groups were randomized by class, and the analysis was done by child. The evidence suggests that zinc deficiency affects behaviour and cognition, but more studies are required to determine a causal relationship with confidence.

Other nutritional deficiencies

Vitamin A deficiency

Vitamin A deficiency is associated with blindness and increased severity of infections such as measles and di-

TABLE 7. Studies of the effect of zinc treatment on children's behavioural and cognitive functions

Source	Sample and study design	Treatment	Outcome	Results
Penland et al. (1997) China [149]	*n* = 372 6–9 yr Double-blind randomized controlled treatment trial; 3 groups	A. 20 mg Zn daily B. 20 mg Zn daily plus micronutrients C. Micronutrients only 10 wk duration	Growth: knee height Neuropsychological functions: visual motor tracking, continuous performance, visual perception, short-term visual memory, concept formation, abstract reasoning, finger tapping	Knee height: B > C > A Neuropsychological findings: significant treatment effect after A or B compared with C for continuous performance, visual perception, visual memory, tracking, concept formation, finger tapping
Bentley (1997) Guatemala [150]	*n* = 108 6–9 mo Double-blind randomized controlled trial	10 mg Zn or placebo 7 mo duration	Behaviour observed at baseline & 3 & 7 mo later	No difference at baseline or 3 mo 7 mo: supplemented group sat & played more, cried less Major milestones not different
Sazawal et al. (1996) India [143]	*n* = 93 children 12–23 mo Double-blind randomized controlled treatment trial	10 mg elemental Zn given daily for 6 mo to treatment group	Behaviour observation for 2 consecutive days, 5 h/day	Significant increase with treatment in high-movement activities Significant treatment effect on children's activity rating score & on energy expenditure score
Cavan et al. (1993) Guatemala [151]	*n* = 162, ~81.5 mo Double-blind randomized controlled treatment trial	Before study all were given multivitamin & mineral supplement without Zn Treatment: 10 mg Zn daily or placebo 25 wk duration	Anthropometry Biochemistry Functional assessments Taste acuity, cell-mediated immunity, cognition (letter sequences, oral directions, design reproduction)	Significant treatment effect for mid-arm circumference & triceps skinfold only, not significant for height & weight No significant treatment effect for functional physiological & cognitive measurements
Friel et al. (1993) Canada [152]	*n* = 52 VLBW infants, mean gestational age 29 wk Randomized controlled treatment trial	Supplemented 6 mo: 11 mg/L Zn, 0.9 mg/L Cu Unsupplemented: 6.7 mg/L Zn, 0.6 mg/L Cu Assessed at 3, 6, 9, 12 mo	Biochemistry: blood & hair samples Anthropometry Cognition: Griffiths developmental assessment	Significant difference in growth velocities & Griffiths motor subscale between supplemented & unsupplemented group No significant difference in Griffiths global score between supplemented & unsupplemented group

continued on next page

TABLE 7. Studies of the effect of zinc treatment on children's behavioural and cognitive functions *(continued)*

Source	Sample and study design	Treatment	Outcome	Results
Gibson et al. (1989) Canada [147]	60 boys aged 5–7 yr Double-blind randomized controlled treatment trial	10 mg Zn daily, or placebo 12 mo duration	Anthropometry: height, weight, weight-for-height Dietary assessment Biochemistry Cognition: 4 subtests of Detroit Tests of Learning Aptitude (sentence imitation, word sequence, oral directions, design reproduction) Hair Zn	No overall treatment effect on anthropometry, biochemistry, or cognition Growth response seen among children who had impaired taste acuity & hair Zn < 1.68 μmol/g at initial assessment

Abbreviation: VLBW, very low birthweight.

arrhoeal disease. The 1995 estimates from the WHO Micronutrient Deficiency Information System database indicate that approximately 2.8 million children under five years of age currently exhibit signs of clinical xerophthalmia, and 14 million pre-school children already have some eye damage from vitamin A deficiency. Blindness would almost certainly have a detrimental effect on children's development, especially where facilities for blind children are lacking.

General conclusions and policy implications

It is only recently that we have begun to understand the large number of different health and nutritional conditions that affect children's development. Their impact appears to spread from gestation through childhood, although some stages are more vulnerable than others.

Several different insults appear to have similar effects on children's behaviour. For example, reduced exploration and activity as well as mood changes appear in protein-energy malnutrition, iron deficiency, and zinc deficiency, as well as illness. In addition, preliminary data show that the stress response system is affected in both iron deficiency and stunting and may be affected by other deficiencies that are currently being investigated. Thus, these children may have difficulty in coping with stressful situations.

Compounding the situation, and at least as important, all these conditions usually occur in deprived environments, which may themselves affect children's behaviour and cognitive development as well as render the children more vulnerable to health and nutritional insults. The data suggest that whereas poor social backgrounds make a child more vulnerable, enriched ones may be protective. It is clear from figure 3 that it is naive to expect that a single intervention (however attached we are to it) will cause significant improvement in children's development (with the exception of iodine in pregnancy).

Health and nutritional professionals and international agencies now need to plan more integrated approaches to programmes that include activities to promote children's psychosocial development as well as their health and nutrition. This calls for a radical revision of current training of health and nutrition professionals so that they can realize their role as promoters of child development rather than only of health and nutrition. We are challenged to come up with a new approach to

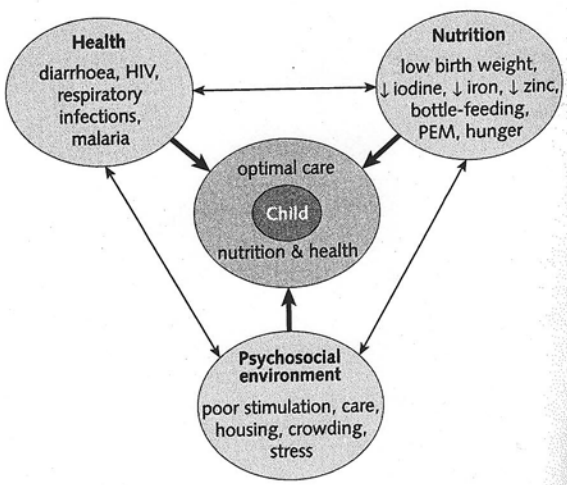

FIG. 3. Some of the multiple risks to child development and the buffering effect of good environments. PEM, protein-energy malnutrition.

child health and nutrition programmes that encompasses improving the psychosocial environment. In order to do this, we need good indicators of both the child's environment and his or her development. We need to pilot and evaluate different approaches and learn from the few projects that are already in progress.

References

1. Stansfield SK, Sheperd DS. Acute respiratory infections. In: Jamison DT, Mosley WH, Measham AR, Bobadilla JL, eds. Disease control priorities in developing countries. 1st ed. New York: Oxford University Press, 1993:67–90.
2. Martines J, Phillips M, Feachem RG. Diarrheal diseases. In: Jamison DT, Mosley WH, Measham AR, Bobadilla JL, eds. Disease control priorities in developing countries. 1st ed. New York: Oxford University Press, 1993:91–116.
3. Najera JA, Liese BH, Hammer J. Malaria. In: Jamison DT, Mosley WH, Measham AR, Bobadilla JL, eds. Disease control priorities in developing countries. 1st ed. New York: Oxford University Press, 1993:281–302.
4. Bundy DA, Cooper ES. Trichuris and trichuriasis in humans. Adv Parasitol 1989;28:107–173.
5. Halloran ME, Bundy DAP, Pollitt E. Infectious disease and the UNESCO basic education initiative. Parasitol Today 1989;5:359–62.
6. Smith AP. Respiratory virus infections and performance. Phil Trans R Soc Lond 1990;327:519–28.
7. Neumann C, McDonald MA, Sigman M, Bwibo N, Marquardt M. Relationships between morbidity and development in mildly to moderately malnourished Kenyan toddlers. Pediatrics 1991;88:934–42.
8. Emond AM, Howat P, Evans JA, Hunt L. The effects of housing on the health of preterm infants. Paediatr Perinat Epidemiol 1997;11:228–39.
9. Clemens J, Albert MJ, Rao M, Huda S, Qadri F, Van Loon FP, Pradhan B, Naficy A, Banik A. Sociodemographic, hygienic and nutritional correlates of *Helicobacter pylori* infection of young Bangladeshi children. Pediatr Infect Dis J 1996;15:1113–18.
10. McCallion WA, Murray LJ, Bailie AG, Dalzell AM, O'Reilly DP, Bamford KB. *Helicobacter pylori* infection in children: relation with current household living conditions. Gut 1996;39:18–21.
11. Watkins WE, Cruz JR, Pollitt E. The effects of deworming on indicators of school performance in Guatemala. Trans R Soc Trop Med Hyg 1996;90:156–61.
12. Connolly KJ, Kvalsvig JD. Infection, nutrition and cognitive performance in children. Parasitology 1993; 107(suppl):S187–200.
13. Kvalsvig JD. The effects of schistosomiasis on spontaneous play activity in black schoolchildren in the endemic areas. An ethological study. S Afr Med J 1981;60:61–4.
14. Loveridge FG, Ross WF, Blair DM. Schistosomiasis: the effect of the disease on educational attainment. South Afr Med J 1948;22:260–3.
15. Nokes C, Grantham-McGregor SM, Sawyer AW, Cooper ES, Robinson BA, Bundy DAP. Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children. Parasitology 1992; 104:537–47.
16. Boivin MJ, Giordani B. Improvements in cognitive performance for schoolchildren in Zaire, Africa, following an iron supplement and treatment for intestinal parasites. J Pediatr Psychol 1993;18:249–64.
17. Simeon DT, Grantham-McGregor SM, Wong MS. *Trichuris trichiura* infection and cognition in children: results of a randomized clinical trial. Parasitology 1995; 110:457–64.
18. Simeon DT, Grantham McGregor SM, Callender JE, Wong MS. Treatment of *Trichuris trichiura* infections improves growth, spelling scores and school attendance in some children. J Nutr 1995;125:1875–83.
19. Callender JE, Grantham McGregor SM, Walker SP, Cooper ES. Treatment effects in Trichuris dysentery syndrome. Acta Paediatr 1994;83:1182–7.
20.. World Health Organization. Vector control of malaria and other mosquito-borne diseases. Report of a WHO study group. Technical Report Series No. 857. Geneva: WHO, 1995.
21. UNICEF. The state of the world's children 1997. New York: Oxford University Press, 1998.
22. Shiff C, Checkley W, Winch P, Premji Z, Minjas J, Lubega P. Changes in weight gain and anaemia attributable to malaria in Tanzanian children living under holoendemic conditions. Trans R Soc Trop Med Hyg 1996;90:262–5.
23. Bradley Moore AM, Greenwood BM, Bradley AK, Bartlett A, Bidwell DE, Voller A, Craske J, Kirkwood BR, Gilles HM. Malaria chemoprophylaxis with chloroquine in young Nigerian children. II. Effect on the immune response to vaccination. Ann Trop Med Parasitol 1985;79:563–73.
24. Abdalla S, Weatherall DJ, Wickramasinghe SN, Hughes M. The anaemia of *P. falciparum* malaria. Br J Haematol 1980;46:171–83.
25. Greenwood BM. Asymptomatic malaria infections—Do they matter? Parasitol Today 1987;3:206–14.
26. Schmutzhard E, Gerstenbrand F. Cerebral malaria in Tanzania. Its epidemiology, clinical symptoms and neurological long term sequelae in the light of 66 cases. Trans R Soc Trop Med Hyg 1984;78:351–3.
27. Bondi FS. The incidence and outcome of neurological abnormalities in childhood cerebral malaria: a long-term follow-up of 62 survivors. Trans R Soc Trop Med Hyg 1992;86:17–19.
28. Muntedam AH, Jaffar S, Bleichrodt N, van Hensbroek M. Absence of neuropsychological sequelae following cerebral malaria in Gambian children. Trans R Soc Trop Med Hyg 1996;90:391–4.
29. Pollitt E. Morbidity and infant development: a hypothesis. Int J Behav Dev 1983;6:461–75.
30. UNICEF. Progress towards universal salt iodization. An update on the current status of universal salt iodization in countries where UNICEF has programmes. New York: UNICEF, 1994.
31. Hetzel BS. Iodine deficiency and fetal brain damage. N Engl J Med 1994;331:1770–1.

32. Obregon MJ, Ruiz de Ona C, Escobar del Ray F, Morreale de Escobar G. Regulation of intracellular thyroid hormone and concentrations in the fetus. In: Delange F, Fisher DA, Glinoer D, eds. Research in congenital hypothyroidism. New York: Plenum, 1989:79–94.
33. Pharoah POD, Connolly KJ. Iodine and brain development. Dev Med Child Neurol 1995;38:464–9.
34. Ferreiro B, Bernal J, Goodyer CG, Branchard CL. Estimation of nuclear thyroid hormone receptor saturation in human fetal brain and lung during early gestation. J Clin Endocrinol Metab 1988;67:853–6.
35. Dumont JE, Ermans AM, Maenhaut FC, Stanbury JB. Large goitre as a maladaptation to iodine deficiency. Clin Endocrinol 1995;43:1–10.
36. Vermiglio F, Lo Presti VP, Argentina GS, Finocchario MD, Gullo D, Squatrito S, Trimarchi F. Maternal hypothyroxinaemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. Clin Endocrinol 1995;42:409–15.
37. Grant DB, Fuggle PW, Smith I. Increased plasma thyroid stimulating hormone in treated congenital hypothyroidism: relation to severity of hypothyroidism, plasma thyroid hormone status, and daily dose of thyroxine. Arch Dis Child 1993;69:555–8.
38. Escobar del Ray F, Obregon MJ, Morreale de Escobar G. Field and experimental studies of iodine deficiency in Spain. In: Delong GR, Robbins J, Condliffe PG, eds. Iodine and the brain. New York: Plenum, 1989:303–15.
39. Sava L, Delange F, Belfiore A, Purrello F, Vigneri R. Transient impairment of thyroid function in newborn from an area of endemic goiter. J Clin Endocrinol Metab 1984;59:90–5.
40. Delange F. Correction of iodine deficiency: benefits and possible side effects. Eur J Endocrinol 1995;132:542–3.
41. Hetzel BS, Potter BJ, Dulberg EM. The iodine deficiency disorders: nature, pathogenesis and epidemiology. In: Bourne GH, ed. Aspects of some vitamins, minerals and enzymes in health and disease. Basel, Switzerland: S. Karger, 1990:59–119.
42. Hetzel BS. Iodine deficiency disorders (IDD) and their eradication. Lancet 1983;2:1126–9.
43. Dunn JT. Extensive personal experience: seven deadly sins in confronting endemic iodine deficiency, and how to avoid them. J Clin Endocrinol Metab 1996;81:1332–5.
44. Muzzo SB, Leiva L. Endemic goiter and cretinism and their control in Chile. In: Dunn JT, Pretell EA, Daza CH, Viteri FE, eds. Toward the eradication of endemic goiter, cretinism, and iodine deficiency. Washington, DC: Pan American Health Organization, 1995.
45. Rani A, Upadhyay SK, Agarwal KN. Intellectual assessment in school children with endemic goitre. Indian Pediatr 1983;20:753–6.
46. Filteau SM, Morris SS, Tomkins AM, Arthur P, Kirkwood BR, Ross DA, Abbott RA, Gyapong JO. Lack of association between vitamin A status and measures of conjunctival epithelial integrity in young children in northern Ghana. Eur J Clin Nutr 1994;48:69–77.
47. Fernald LC. Iodine deficiency and mental development in children. In: Nutrition, health, and child development. Research advances and policy recommendations. PAHO Scientific Publication No. 566. Washington, DC: Pan American Health Organization, The World Bank, and Tropical Metabolism Research Unit University of the West Indies, 1998:234–55.
48. Azizi F, Kalani H, Kimiagar M, Ghazi A, Sarshar A, Nafarabadi M, Rahbar N, Noohi S, Mohajer M, Yassai M. Physical, neuromotor and intellectual impairment in non-cretinous schoolchildren with iodine deficiency. Int J Vitam Nutr Res 1995;65:199–205.
49. Tiwari BD, Godbole MM, Chattopadhyay N, Mandal A, Mithal A. Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. Am J Clin Nutr 1996;63:782–6.
50. Azizi F, Nafarabadi M, Ghazi A, Kimiagar M, Noohi S, Rahbar N, Bahrami A, Kalantari S. Impairment of neuromotor and cognitive development in iodine-deficient schoolchildren with normal physical growth. Acta Endocrinol 1993;129:501–4.
51. Vermiglio F, Sidoti M, Finocchario MD, Battiato S, Lo Presti VP, Benvenga S, Trimarchi F. Defective neuromotor and cognitive ability in iodine-deficient schoolchildren of an endemic goiter region in Sicily. J Clin Endocrinol Metab 1990;70:379–84.
52. Fenzi GF, Giusti LF, Aghini-Lombardi F, Marcocci C, Santini F, Bargagna S, Brizzolara D, Ferretti G, Falciglia G, Monteleone M, Marcheschi M, Pinchera A. Neuropsychological assessment in school children from an area of moderate iodine deficiency. J Endocrinol Invest 1990;13:427–31.
53. Boyages SC, Collins JK, Maberly GF, Jupp JJ, Morris J, Eastman CJ. Iodine deficiency impairs intellectual and neuromotor development in apparently-normal persons. Med J Aust 1989;150:676–82.
54. Bleichrodt N, Garcia I, Rubio C, Morreale de Escobar G, Ecobar del Rey F. Developmental disorders associated with severe iodine deficiency. In: Hetzel B, Dunn J, Stanbury J, eds. The prevention and control of iodine deficiency disorders. Amsterdam: Elsevier, 1987:65–84.
55. Mehta M, Pandav CS, Kochupillai N. Intellectual assessment of school children from severely iodine deficient villages. Indian Pediatr 1987;24:467–73.
56. Querido A, Bleichrodt N, Djokomoeljanto R. Thyroid hormones and human mental development. Prog Brain Res 1978;48:337–44.
57. Bleichrodt N, Resing W. Measuring intelligence and learning potential in iodine-deficient and non-iodine deficient populations. In: Stanbury JB, ed. The damaged brain of iodine deficiency. New York: Cognizant Communication, 1994:37–42.
58. Chaouki ML, Benmiloud M. Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. Eur J Endocrinol 1994;130:547–51.
59. Pedersen KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS, Karsen KR, Eriksen GM, Johannsesn PL. Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. J Clin Endocrinol Metab 1993;77:1078–83.
60. Ramirez I, Fierro-Benitez R, Estrella E, Jaramillo C, Diaz C, Urresta J. Iodized oil in the prevention of endemic goiter and associated defects in the Andean region of Ecuador. II. Effects on neuromotor development and somatic growth before two years. In: Stanbury JB, ed. Endemic goiter. Washington, DC: Pan American Health Organization, 1969:341–59.

61. Ramirez I, Fierro-Benitez R, Estrella E, Jaramillo C, Diaz C, Urresta J. The results of prophylaxis of endemic cretinism with iodized oil in rural Andean Ecuador. I. In: Stanbury JB, Kroc RL, eds. Human development and the thyroid gland. Relation to endemic cretinism. New York: Plenum Press, 1972:223–37.
62. Pretell EA, Torres T, Zenteno V, Cornejo M. Prophylaxis of endemic goiter with iodized oil in rural Peru. Adv Exp Med Biol 1972;30:249–65.
63. Thilly CH, Lagasse R, Roger G, Bourdoux P, Ermans AM. Impaired fetal and postnatal development and high perinatal death-rate in a severe iodine deficient area. In: Stockigt JR, Nagataki S, eds. Thyroid research VIII. Oxford: Pergamon, 1980:20–3.
64. Cao X-Y, Jiang X-M, Dou Z-H, Murdon AR, Zhang M-L, O'Donnell K, Tai M, Amette K, DeLong N, Delong GR. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med 1994;331:1739–44.
65. Pharoah POD, Buttfield IH, Hetzel BS. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 1971;1:308–10.
66. Connolly KJ, Pharaoh POD, Hetzel BS. Fetal iodine deficiency and motor performance during childhood. Lancet 1979;2:1149–51.
67. Pharoah POD, Connolly KJ, Hetzel BS, Ekins RP. Maternal thyroid function and motor competence in the child. Dev Med Child Neurol 1981;23:76–82.
68. Pharoah POD, Connolly KJ, Ekins RP, Harding AG. Maternal thyroid hormone levels in pregnancy and the subsequent cognitive and motor performance of the children. Clin Endocrinol 1984;21:265–70.
69. Connolly KJ, Pharoah POD. Iodine deficiency, maternal thyroxine levels in pregnancy and developmental disorders in the children. In: Delong GR, Robbins J, Condliffe PG, eds. Iodine and the brain. New York: Plenum, 1989:317–31.
70. Greene LS. A retrospective view of iodine deficiency, brain development, and behavior from studies in Ecuador. In: Stanbury JB, ed. The damaged brain of iodine deficiency. New York: Cognizant Communication, 1994:173–86.
71. Trowbridge FL. Intellectual assessment in primitive societies, with a preliminary report of a study of the effects of early iodine supplementation on intelligence. Adv Exp Med 1972;30:137–59.
72. Pharoah POD, Connolly KJ. A controlled trial of iodinated oil for the prevention of endemic cretinism: a long term follow-up. Int J Epidemiol 1987;16:68–73.
73. Pharoah POD, Connolly KJ. Maternal thyroid hormones and fetal brain development. In: Delong GR, Robbins J, Condliffe PG, eds. Iodine and the brain. New York: Plenum, 1989:333–54.
74. Pharoah POD, Connolly KJ. Effects of maternal iodine supplementation during pregnancy. Arch Dis Child 1991;66:145–7.
75. Pharoah POD, Connolly KJ. Iodine deficiency in Papua New Guinea. In: Stanbury JB, ed. The damaged brain of iodine deficiency. New York: Cognizant Communication, 1994:299–308.
76. Wang YY, Yan SH. Improvement in hearing among otherwise normal schoolchildren in iodine-deficient areas of Guizhou, China, following use of iodised salt. Lancet 1985;2:518–20.
77. Dodge PR, Palkes H, Fierro-Benitez R, Ramirez I. Effect on intelligence of iodine in oil administered to young Andean children—a preliminary report. In: Stanbury JB, ed. Endemic goiter. Washington, DC: Pan American Health Organization, 1969:378–80.
78. Bleichrodt N, Escobar del Ray F, Morreale de Escobar G, Garcia I, Rubio C. Iodine deficiency, implications for mental and psychomotor development in children. In: Delong GR, Robbins J, Condliffe PG, eds. Iodine and the brain. New York: Plenum, 1989: 259–87.
79. Bautista A, Barker PA, Dunn JT, Sanchez M, Kaiser DL. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. Am J Clin Nutr 1982;35:127–34.
80. Shrestha RM. Effect of iodine and iron supplementation on physical, psychomotor and mental development in primary school children in Malawi. Wageningen, Netherlands: Grafisch Service Centrum, 1994.
81. Dunn JT. Iodine deficiency—the next target for elimination? N Engl J Med 1992;326:267–8.
82. Gruters A, Liesenkotter KP, Willgerodt H. Persistence of differences in iodine status in newborns after the reunification of Berlin [letter]. N Engl J Med 1996;333:1429.
83. World Health Organization. Safe use of iodized oil to prevent iodine deficiency in pregnant women. Bull WHO 1996;74:1–3.
84. Elnagar B, Eltom M, Karlsson FA, Ermans AM, Gebre-Medhin M, Bourdoux PP. The effects of different doses of oral iodized oil on goiter size, urinary iodine, and thyroid related hormones. J Clin Endocrinol Metab 1996;80:891–7.
85. Benmiloud M, Chaouki ML, Gutekunst R, Teichert H-M, Wood WG, Dunn JT. Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. J Clin Endocrinol Metab 1994;79:20–4.
86. Ermans AM. Prevention of iodine deficiency disorders by oral iodized oil. Eur J Endocrinol 1994;130:545–6.
87. Dunn JT, Thilly CH, Pretell EA. Iodized oil and other alternatives to iodized salt for the prophylaxis of endemic goiter and cretinism. In: Dunn JT, Pretell EA, Daza CH, Viteri FE, eds. Towards the eradication of endemic goitre, cretinism and iodine deficiency. PAHO Scientific Publication No. 52. Washington, DC: Pan American Health Organization, 1986:170–81.
88. DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the world. World Health Stat Q 1985;38:302–16.
89. USAID. Iron interventions for child survival. London: OMNI/USAID, 1995.
90. Scrimshaw NS. Functional consequences of iron deficiency in human populations. J Nutr Sci Vitaminol 1984;30:47–63.
91. Bhatia D, Seshadri S. Anemia, undernutrition and physical work capacity of young boys. Indian Pediatr 1987;24: 133–9.
92. Webb TE, Oski FA. Behavioral status of young adolescents with iron deficiency anemia. J Special Educ 1974; 8:153–6.
93. Webb TE, Oski FA. Iron deficiency anemia and scholastic achievement in young adolescents. J Pediatr 1973;82:827–30.
94. Grindulis H, Scott PH, Belton NR, Wharton BA. Combined deficiency of iron and vitamin D in Asian toddlers. Arch Dis Child 1986;61:843–8.

95. Ivanovic D, Vasquez M, Marambio M, Ballester D, Zacarias I, Aguayo M. Nutrition and education. II. Educational achievement and nutrient intake of Chilean elementary and high school graduates. Arch Latinoam Nutr 1991;41:499–515.
96. Popkin B, Lim-Ybanez M. Nutrition and school achievement. Soc Sci Med 1982;16:53–61.
97. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anemic infants treated with iron. Lancet 1993;341:1–4.
98. Lozoff B, Brittenham GM, Viteri FE, Wolf AW, Urrutia JJ. The effects of short-term oral iron therapy on developmental deficits in iron deficient anemic infants. J Pediatr 1982;100:351–7.
99. Walter T. Developmental deficits in iron deficient infants: effects of age and severity of iron lack. J Pediatr 1983;102:519–22.
100. Lozoff B, Brittenham GM, Wolf AW. Iron deficiency anemia and iron therapy: effects on infant developmental test performance. Pediatrics 1987;79:981–95.
101. Lozoff B, Wolf AW, Jimenez E. Iron-deficiency anemia and infant development: effects of extended oral iron therapy. J Pediatr 1996;129:382–9.
102. Johnson DL, McGowan TJ. Anaemia and infant behavior. Nutr Behav 1983;1:185–92.
103. Deinard AS, List A, Lindgren B, Hunt JV, Chang PN. Cognitive deficits in iron-deficient and iron-deficient anemic children. J Pediatr 1986;108:681–9.
104. Walter T, de Andraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. Pediatrics 1989;84:7–17.
105. Wasserman G, Graziano JH, Factor Litvak P, Popovac D, Morina N, Musabegovic A, Vrenezi N, Capuni Paracka S, Lekic V, Preteni Redjepi E. Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. J Pediatr 1992;121:695–703.
106. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991;325:687–94.
107. de Andraca I, Walter T, Castillo M, Pino P, Rivera P, Cobo C. Iron deficiency anemia and its effects upon psychological development at preschool age: a longitudinal study. Nestlé Foundation Annual Report. Lausanne, Switzerland: Nestlé Foundation, 1990;53–62.
108. Palti H, Meijer A, Adler B. Learning achievement and behavior at school of anemic and non-anemic infants. Early Hum Dev 1985;10:217–23.
109. Cantwell RJ. The long term neurological sequelae of anemia in infancy. Pediatr Res 1974;342:68.
110. Palti H, Pevsner B, Adler B. Does anemia in infancy affect achievement on developmental and intelligence tests? Hum Biol 1983;55:183–94.
111. Walter T. Impact of iron deficiency on cognition in infancy and childhood. Eur J Clin Nutr 1993;47:307–16.
112. Czajka-Narins DM, Haddy TB, Kallen DJ. Nutrition and social correlates in iron deficiency anemia. Am J Clin Nutr 1978;31:955–60.
113. Oski FA, Honig AS. The effects of therapy on the developmental scores of iron-deficient infants. J Pediatr 1978;92:21–5.
114. Aukett M, Parks Y, Scott P, Wharton B. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child 1986;61:849–57.
115. Heywood A, Oppenheimer S, Heywood P, Jolley D. Behavioral effects of iron supplementation in infants in Madang, Papua New Guinea. Am J Clin Nutr 1989;50: 630–7.
116. Moffatt MEK, Longstaffe S. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomized clinical trial. J Pediatr 1994;125:577–8.
117. Lozoff B, de Andraca I, Walter T, Pino P. Does preventing iron-deficiency anemia (IDA) improve developmental test scores? Pediatr Res 1996;39:136(A).
118. Morley R. Food for the infant's brain. Br Nutr Found Bull 1998;23:65–76.
119. Seshadri S, Gopaldes T. Impact of iron supplementation on cognitive functions in preschool and school-aged children: the Indian experience. Am J Clin Nutr 1989;50:675–86.
120. Soewondo S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. Am J Clin Nutr 1989;50: 667–74.
121. Soemantri AG. Preliminary findings on iron supplementation and learning achievement of rural Indonesian children. Am J Clin Nutr 1989;50:698–702.
122. Soemantri AG, Pollitt E, Kim I. Iron deficiency anemia and educational achievement. Am J Clin Nutr 1985;42: 1221–8.
123. Pollitt E, Soemantri AG, Yunis F, Scrimshaw NS. Cognitive effects of iron-deficiency anaemia [letter]. Lancet 1985;1:158.
124. Pollitt E, Hathirat P, Kotchabhakdi NJ, Missell L, Valyasevi A. Iron deficiency and educational achievement in Thailand. Am J Clin Nutr 1989;50:687–97.
125. Lozoff B. Explanatory mechanisms for poorer development in iron-deficient anemic infants. In: Grantham-McGregor SM, ed. Nutrition, health, and child development: research advances and policy implications. Washington, DC: Pan American Health Organization, 1998:162–78.
126. Dallman PR, Spirito RA. Brain iron in the rat: extremely slow turnover in normal rats may explain long-lasting effects of early iron deficiency. J Nutr 1977;107:1075–81.
127. Ben Shachar D, Ashkenazi R, Youdim MB. Long-term consequence of early iron-deficiency on dopaminergic neurotransmission in rats. Int J Dev Neurosci 1986; 4:81–8.
128. Youdim MB. Neuropharmacological and neurobiochemical aspects of iron deficiency. In: Dobbing J, ed. Brain, behaviour, and iron in the infant diet. London: Springer-Verlag, 1990:83–106.
129. Lozoff B, Wolf AW, Urrutia JJ, Viteri FE. Abnormal behavior and low developmental test scores in iron-deficient anemic infants. J Dev Behav Pediatr 1985;6:69–75.
130. Lozoff B, Klein NK, Prabucki KM. Iron-deficient anemic infants at play. J Dev Behav Pediatr 1986;7:152–8.
131. Grantham-McGregor SM, Fernald LC, Sethuraman K. The effects of health and nutrition on cognitive and behavioural

development in children in the first three years of life. Part 1. Low birth weight, breastfeeding, and protein-energy malnutrition. Food Nutr Bull 1999;20:53–75
132. Levitsky DA. Malnutrition and hunger to learn. In: Levitsky DA, ed. Malnutrition, environment and behavior. Ithaca, NY, USA: Cornell University Press, 1979:161–79.
133. Fox NA, Porges SW. The relation between neonatal heart period patterns and developmental outcome. Child Dev 1985;56:28–37.
134. Porges SW, Matthews KA, Pauls DL. The biobehavioral interface in behavioral pediatrics. Pediatrics 1992;90: 789–97.
135. Yip R, Parvanta I, Scanlon K, Borland EW, Russell CM, Trowbridge FL. Pediatric nutrition surveillance system—United States, 1980–1991. MMWR CDC Surveill Summ 1992;41:1–24.
136. Booth IW, Aukett MA. Iron deficiency anaemia in infancy and early childhood. Arch Dis Child 1997;76:549–53.
137. United Nations Administrative Committee on Coordination/Subcommittee on Nutrition. Third report on the World Nutrition Situation. Geneva: ACC/SCN, 1997.
138. Layrisse M, Chaves JF, Mendez Castellano, Bosch V, Tropper E, Bastardo B, Gonzalez E. Early response to the effect of iron fortification in the Venezuelan population. Am J Clin Nutr 1996;64:903–7.
139. Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. Nutr Rev 1997;55:223–32.
140. Sandstead HH. Is zinc deficiency a public health problem? Nutrition 1995;11:87–92.
141. Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, Hauth JC. The effect of zinc supplementation on pregnancy outcome. JAMA 1995; 274:463–8.
142. Castillo Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth and immune function. Am J Clin Nutr 1987;45:602–8.
143. Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK. Effect of zinc supplementation on observed activity in low socio-economic Indian preschool children. Pediatrics 1996;98:1132–7.
144. Walravens PA, Krebs N, Hambidge KM. Linear growth of low income preschool children receiving a zinc supplement. Am J Clin Nutr 1983;38:195–201.
145. Walravens PA, Hambidge KM, Koepfer DM. Zinc supplementation in infants with a nutritional pattern of failure to thrive: a double-blind, controlled study. Pediatrics 1989;83:532–8.
146. Ninh NX, Thissen JP, Collette L, Gerard G, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. Am J Clin Nutr 1996;63:514–9.
147. Gibson RS, Smit Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc deficiency syndrome in some Southern Ontario boys with low height percentiles. Am J Clin Nutr 1989;49: 1266–73.
148. Golub MS, Keen CL, Gershwin ME, Hendrickx AG. Developmental zinc deficiency and behavior. J Nutr 1995;125:2263S–71S.
149. Penland JG, Sandstead HH, Alcock NW, Dayal HH, Chen XC, Li JS, Zhao F, Yang JJ. A preliminary report: effects of zinc and micronutrient repletion on growth and neuropsychological function of urban Chinese children. J Am Coll Nutr 1997;16:268–72.
150. Bentley ME, Caulfield LE, Ram M, Santizo MC, Hurtado E, Rivera JA, Ruel MT, Brown KH. Zinc supplementation affects the activity patterns of rural Guatemalan infants. J Nutr 1997;127:1333–8.
151. Cavan KR, Gibson RS, Graziosa CF, Isalgue AM, Ruz M, Solomons NW. Growth and body composition of peri-urban Guatemalan children in relation to zinc status: a longitudinal zinc intervention trial. Am J Clin Nutr 1993;57:344–52.
152. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, McKim E, Zerbe GO. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr 1993;17:97–104.