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Child development: risk factors for adverse outcomes in developing countries

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Poverty and associated health, nutrition, and social factors prevent at least 200 million children in developing countries from attaining their developmental potential. We review the evidence linking compromised development with modifiable biological and psychosocial risks encountered by children from birth to 5 years of age. We identify four key risk factors where the need for intervention is urgent: stunting, inadequate cognitive stimulation, iodine deficiency, and iron deficiency anaemia. The evidence is also sufficient to warrant interventions for malaria, intrauterine growth restriction, maternal depression, exposure to violence, and exposure to heavy metals. We discuss the research needed to clarify the effect of other potential risk factors on child development. The prevalence of the risk factors and their effect on development and human potential are substantial. Furthermore, risks often occur together or cumulatively, with concomitant increased adverse effects on the development of the world's poorest children.

Introduction

The first paper in this series showed that more than 200 million children under 5 years of age in developing countries are not fulfilling their developmental potential.[1] In this paper, we review biological and psychosocial risk factors that contribute to these adverse outcomes. We use the term risk factor to refer to biological and psychosocial hazards that can compromise development.

Figure 1 shows pathways from poverty to poor child development. Development consists of linked domains of sensori-motor, cognitive-language, and social-emotional function.[2] Poverty and the socio-cultural context increase young children's exposure to biological and psychosocial risks that affect development through changes in brain structure and function, and behavioural changes. Although we consider risks individually in this paper, children are frequently exposed to multiple and cumulative risks.[3] As risks accumulate, development is increasingly compromised. Data from Guatemala[4] (figure 2) show a linear decrease in adolescents' school achievement and cognition with an increase in risk factors encountered by age 3 years.

As discussed in the first paper in this series,[1] children's ability on school entry is an important component in determining their progress in school. We therefore focus on risk factors in early childhood that affect readiness for school and subsequent school performance. School readiness is affected by cognitive ability, social-emotional competence (affects classroom behaviour and peer relations), and sensori-motor development (affects critical skills such as writing).[5]

We first review the effect on development of individual biological and psychosocial risk factors. Based on this review we identify key risk factors which should be the main focus for interventions. The remaining risks are grouped into those where the evidence is sufficient to warrant implementation of interventions and those where additional information is needed.

Biological risk factors for child development

Nutrition

Intrauterine growth restriction

Intrauterine growth restriction indicates constraints in fetal nutrition during a crucial period for brain development. In developing countries, intrauterine growth restriction is mainly due to poor maternal nutrition and infections. This review is restricted to infants at term with low birthweight (birthweight <2500 g; ≥37 weeks' gestation), which makes up 11% of births in developing countries.[10]

At age 12 months, low-birthweight infants with intrauterine growth restriction in Brazil had lower developmental levels than infants with birthweight 3000–3499 g.[11] Term low-birthweight infants in Guatemala had lower cognitive scores at age 2 and 3 years,[12,13] and in Jamaica had poorer problem solving ability at 7 months[14] and lower developmental levels at 15 and 24 months,[15] than infants with normal birthweight (≥2500 g). Effect sizes from these studies are shown in figure 3. In Brazil and Jamaica, low-birthweight infants were also rated as less active, vocal, happy, or cooperative, and in Brazil more inhibited, than infants with normal birthweight.[11,14]

In developed countries, the effects of intrauterine growth restriction are reported to remain into adolescence and adulthood.[16] However, only the Guatemala study has follow-up to these ages and no significant differences were found.[17,18] A study in China suggests that, controlling for gestational age, infants with low birthweight are at greater risk of behavioural problems in adolescence than infants with normal birthweight.[19]

Food supplementation for pregnant women in Taiwan benefited child motor development at 8 months but not mental development or intelligence quotient (IQ) at

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5 years.[20] In Colombia, supplementation of mothers in the third trimester of pregnancy and infants up to age 6 months did not benefit developmental levels from age 6 months to 3 years.[21]

Sample sizes for low-birthweight infants with intrauterine growth restriction were small to moderate in the cohort studies reviewed. Nonetheless, they consistently indicate deficits in such infants up to age 3 years. There is need for more data for longer-term outcomes and for inclusion of developmental outcomes
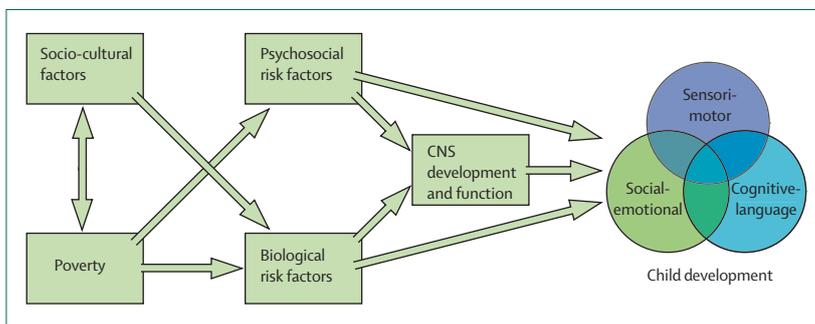
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Figure 1: Pathways from poverty to poor child development
Socio-cultural risk factors include gender inequity, low maternal education, and reduced access to services. Biological risks include prenatal and postnatal growth, nutrient deficiencies, infectious diseases, and environmental toxins. Psychosocial risks include parenting factors, maternal depression and exposure to violence. Consequences of impairments in child development are likely to be inter-generational (not shown in figure). Poorly developing children are likely to remain in poverty as adults,[1] thus continuing the pathways shown for their offspring.

in assessments of interventions aimed at increasing birthweight.

Childhood undernutrition
Early work linking undernutrition and child development focused on severe clinical malnutrition. A comprehensive review indicated generally consistent findings, with deficits in intelligence and school performance continuing to adolescence compared with control children.[22]

A third of children younger than 5 years in developing countries have linear growth retardation or stunting,[9] defined as height-for-age below −2 SD of reference values. Stunting is a measure of chronic undernutrition and is caused by poor nutrition often compounded by infectious diseases. We first consider evidence linking undernutrition defined in terms of growth and child development with emphasis on studies of stunting, and then the effects of specific micronutrient deficiencies.

The association between stunting and development was reviewed in detail in the first paper in this series.[1] Controlling for socio-economic covariates, prospective cohort studies consistently show significant associations between stunting by age 2 or 3 years and later cognitive deficits,[23–26] school achievement, and dropout.[24,26-28] Figure 4 shows effects on IQ through to age 18 years in stunted Jamaican children. The presence of cognitive and educational deficits in stunted children is a consistent and robust finding, although the size of the deficit varies across studies.

In young children, underweight and stunting are also associated with apathy, less positive affect,[29] lower levels of play,[29,30] and more insecure attachment[30] than in non-growth-retarded children. Longitudinal studies show more problems with conduct, poorer attention, and poorer social relationships at school age.[27,31,32]

Randomised trials that provide food supplements to improve children's nutritional status and development show concurrent benefits to motor development,[21,33–36] mental development[21,33,36] and cognitive ability.[35] Where reported, gains during intervention range from 6–13 developmental quotient (DQ) points compared with controls. Two examples are shown in figure 5. Benefits to behaviour include reduced apathy[37] and less fussiness[36] but have not always been reported.[29] Details of the trials are given in webtable 1.

Less information is available on long-term benefits. In two studies where supplementation was provided to children who were already undernourished, follow-up after the intervention showed limited[38] or no benefits to cognition or behaviour.[26,27] However, the intervention period was only 3 months in one study, and in the other study, the achieved increases in intakes were less than targeted. Larger benefits to later cognition and educational outcomes were seen in a Guatemalan study where supplementation began during pregnancy and offspring were supplemented through at least the first 2 years of life.[35] Additionally, children who received higher levels of

supplementation from birth to 2 years showed greater social involvement and less anxiety at age 6–8 years.[39] Benefits to current cognitive development from supplementation have been consistent across studies but benefits to behaviour are less consistent. Evidence suggests that long-term benefits might be more likely with a preventive approach.

Iodine deficiency

Iodine is a constituent of thyroid hormones, which affect central nervous system development and regulate many physiological processes.[40] Worldwide, 35% of people (1990 million) have insufficient iodine intake.[41] Although a worldwide programme to reduce iodine deficiency through salt iodisation has produced substantial progress,[9] the condition continues to threaten the development of many children.

Iodine deficiency can lead to congenital hypothyroidism and irreversible mental retardation, making it the most common preventable cause of mental retardation.[40,42,43] Previous research has focused on subclinical iodine deficiency.[42,43,44] A 1994 meta-analysis of 18 studies of children and adolescents concluded that IQ scores averaged 13·5 points lower with iodine deficiency (0.9 SD).[45] A 2005 meta-analysis of 37 studies in Chinese publications, which included 12 291 children younger than 16 years, concluded that IQs averaged 12·5 points lower for children growing up in iodine deficient areas than in sufficient areas.[46] Children who received iodine supplementation prenatally and postnatally averaged 8·7 points higher than those who did not.[46] Thus, results of both meta-analyses are congruent, although studies of varying quality were included. A longitudinal study in China that assessed timing of supplementation showed that iodine supplementation in the first and second trimesters of pregnancy decreased the prevalence of moderate and severe neurological abnormalities and increased developmental test scores through 7 years, compared with supplementation later in pregnancy or treatment after birth.[47,48] This overwhelming evidence makes prevention of iodine deficiency a high global priority to foster children's development.

Iron deficiency

The estimated prevalence of anaemia in children younger than 4 years in developing countries is 46–66%, half of which is thought to be iron deficiency anaemia.[49] In animal (rodent) models, early iron deficiency anaemia—before and after iron repletion— alters brain metabolism and neurotransmission, myelination, and gene and protein profiles.[50] Prenatal iron deprivation in non-human primates altered activity, impulsivity, and wariness; postnatal iron deprivation impaired emotional and cognitive development.[51]

19 of 21 studies reported poorer mental, motor, social-emotional, or neurophysiologic functioning in infants with iron deficiency anaemia than those without, despite variation in study sample size and quality.[50,52] Six studies in
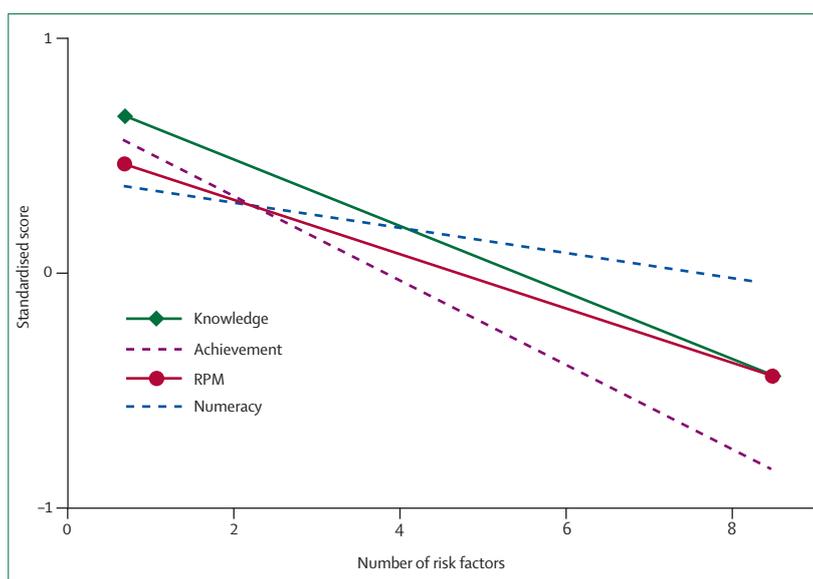
Figure 2: Relation between risk factors in early childhood in Guatemalan children and achievement scores in adolescence
Numeracy (mathematics skills) and general knowledge scores derived from a standardised achievement test. RPM=child's score on a non-verbal test of intelligence (Raven's Progressive Matrices). Achievement=child's summed score on a standardised test of reading comprehension and vocabulary. A median split was used to classify children as high or low risk on each of eight biological and psychosocial risk factors. Children classified as high risk on a given factor received a score of 1 for that factor, whereas children classified as low risk received a score of 0. The number of risk factors is the summed score for each child across the eight risk factors. Figure adapted with permission from: Gorman K, Pollitt E. Does schooling buffer the effects of early risk? *Child Dev* 1996; **67:** 314–26. Copyright: Blackwell Publishing Ltd.
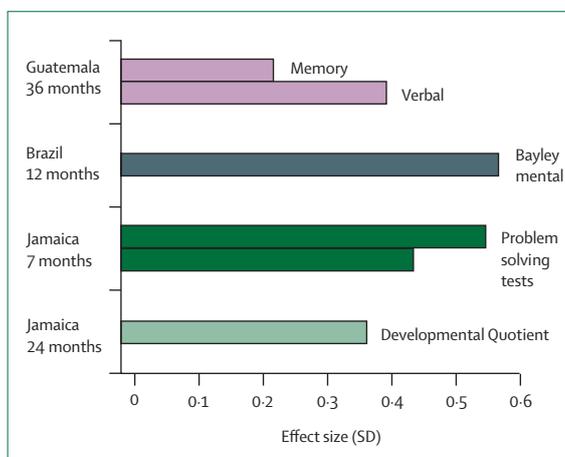
Figure 3: Effect size (SD) for comparisons of children born with or without intrauterine growth restriction at term
Effects sizes were calculated from data reported in Guatemala,[12] Brazil,[11] and Jamaica.[14,15] The larger the effect size, the greater the deficit.

developing countries used standardised tests to assess mental and motor performance before and after a full course of iron therapy in full-term infants with iron deficiency anaemia who were otherwise well-nourished (webtable 2).[53–58] Infants with iron deficiency anaemia showed lower pretreatment mental scores in all six studies (6–15 points lower [0·5–1·3 SD]), lower motor scores in five studies[53–56,58] (6–17 points lower [0·7–1·1 SD]), and

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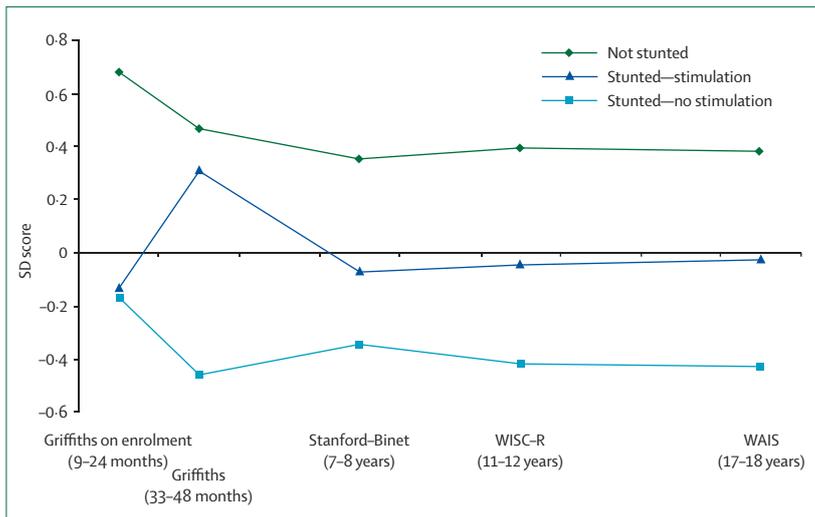
Figure 4: DQ or IQ scores of stunted and non-stunted Jamaican children from age 9–24 months to 17–18 years
Figure shows long-term deficits associated with stunting and the sustained benefits to stunted children who received a home-visiting programme providing early childhood stimulation. WISC-R=Wechsler Intelligence Scale for Children—revised. WAIS=Wechsler Adult Intelligence Scale. Reproduced with permission from Walker SP, Chang SM, Powell CA, Grantham-McGregor SM. Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: prospective cohort study. *Lancet* 2005; **366:** 1804–07.

Figure 5: Effects of food supplementation given to stunted children (Jamaica[33]) or to pregnant women and their offspring through age 3 years (Bogota, Colombia[21]) on developmental levels (DQ)
Data points represent mean values reported in the papers.

altered social-emotional outcomes in three of three studies than infants without such anaemia.[57–59] In four of these studies, poorer scores 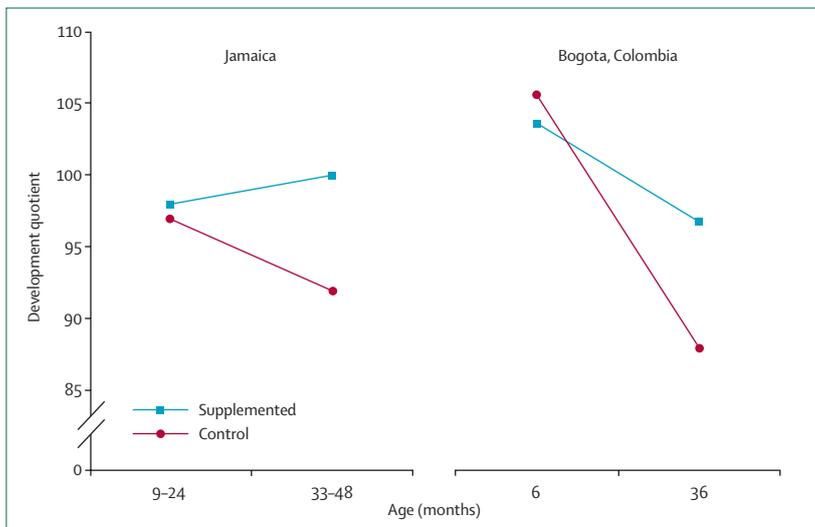in infants with iron deficiency anaemia persisted after 3 months of therapy,[54,56–58] whereas in two studies marked improvements were seen.[53,55] In preschool-aged children with iron deficiency anaemia, improved cognitive outcome with iron treatment has been consistently reported.[52,60]

Importantly, we must distinguish between studies in which children meeting haematology criteria are assigned to treatment, including therapeutic doses of iron (so-called treatment studies), from studies in which children are assigned to supplemental iron (lower doses) irrespective of initial iron status (supplementation trials). Smaller effect sizes in supplementation trials are meaningful, in view of the unselected nature of the samples. In addition to preventive trials in developed countries,[61–64] there are five large trials of iron supplementation in infants or young children in developing countries (table 1). Four included infants at risk for stunting,[65–68] often assessing iron with or without other micronutrients, and one included healthy, well-nourished infants.[69] All reported benefits of iron for motor outcomes (one only in combination with zinc[66]), three reported social-emotional benefits,[65,66,69] and cognitive-language benefits were seen in two studies.[68,69] Effect sizes were generally 0·30–0·40 SD. A systematic review[60] that reported no effect of iron in infants did not include several of these studies and did not separate studies of iron treatment for 7–10 days from full-course therapy or treatment studies from supplementation trials.

Ten follow-up reports compared children who had iron deficiency anaemia or other indication of chronic severe iron deficiency in infancy with those without. Intervals after iron therapy in infancy ranged up to young adulthood. Though studies varied in quality, all found poorer outcome in former iron deficient anaemic or chronically iron-deficient individuals,[50] including long-term effects on IQ (estimated 1·73 points lower for each 10 g/L decrease in haemoglobin in a meta-analysis[49]) and lower motor scores, more grade repetition, anxiety or depression, social problems, and inattention in adolescence[70] and a widening gap in cognitive scores to 19 years,[71] despite iron therapy that corrected their anaemia in infancy. Figure 6 shows the combined effect on cognitive scores of chronic iron deficiency in infancy and cumulative environmental risk in the longest available follow-up study (Costa Rica).[71] As yet there are no long-term follow-ups of supplementation trials. However, the short-term improvements seen in iron-supplemented infants suggest that adverse effects can be prevented, reversed, or both, with iron earlier in development or before iron deficiency becomes severe or chronic.

There is conclusive evidence that infants with iron deficiency anaemia are developmentally at risk in the short term and consistent evidence that they continue to be so in the long term despite iron therapy. Large supplementation trials in infants in developing countries show benefits of iron, especially on motor and social-emotional outcomes (table 1), which holds promise that long-term effects can be prevented with supplementation. In preschool-aged children with iron deficiency anaemia, iron treatment improves short-term cognitive outcome.

Other nutritional factors
We review effects of breastfeeding and zinc on development. Other micronutrients such as vitamins A

	Sample	Supplementation	Outcomes	Important benefits of iron	Comments
Zanzibar[68]	High prevalence of stunting and anaemia 6–59 months at enrolment, n=614 n=538 at study completion.	Daily iron (10 mg) or placebo, anthelmintic treatment every 3 months or placebo. Duration: 12 months.	Parent report of gross motor and language milestones.	Improved language development (0·8 points on 20-point scale). Improved motor development in children with low baseline haemoglobin (1·1 points on 18-point scale).	Large age range. Relatively crude outcome measure.
Chile[69]	Full-term, healthy well-nourished infants n=1798 at age 6 months at enrolment, n=1657 at study completion. High and low iron similar in 12-month outcomes, combined (n=1123) and compared to no added iron (n=534).	Three treatments (daily): In first years of study, high (12 mg/L) or low (2·3 mg/L) iron formula for infants on at least one bottle per day. In last years of study, high iron formula or no added iron (cow milk +vitamins) for infants on at least one bottle per day; exclusively breastfed infants assigned to vitamins with or without iron (15 mg per day). Duration: 6 months.	Bayley mental development index (MDI), psychomotor index (PDI), and behaviour rating scales (BRS), Fagan at 12 months, age of crawling.	Shorter looking times on Fagan. Crawled earlier. More positive affect, social referencing and social interaction, soothing by words or objects when upset, resisting giving up toys and test materials; less tremulous. Effect size 0.32 SD for social-emotional.	Not a simple double blind RCT due to changes mid-study.
Bangladesh[66]	High prevalence of stunting and anaemia 6 months at enrolment, n=346. n=221 at study completion.	Five treatments (weekly): iron (20mg), zinc (20 mg), iron plus zinc, multimicronutrients, or riboflavin (placebo). Duration: 6 months.	Bayley MDI, PDI, BRS at 12 months.	Less decrease in PDI (iron and zinc or multi-micronutrient vs riboflavin) Effect sizes 0·35 and 0·39 SD. Better orientation-engagement (iron, zinc, or iron plus zinc vs riboflavin). Effect sizes 0·30–0·41 SD.	Effect of iron per se clearest for orientation engagement.
Indonesia[67]	High prevalence of stunting and anaemia Younger than 6 months at enrolment, n=680. n=655 completing developmental study.	Four treatments (daily): iron (10 mg), zinc (10 mg), iron plus zinc, placebo. Duration: 6 months.	Bayley MDI, PDI, BRS at age 12 months.	Higher PDI (iron vs placebo). Effect size 0·27 SD.	
India[65]	High prevalence of stunting and anaemia. Full-term small-for-gestational age infants. Enrolled at birth, subset at 15 months, n=439.	Four treatments, starting at age 1 month (daily): micronutrient mix containing iron; micronutrient mix without zinc; riboflavin plus zinc; or riboflavin only (placebo). Duration: 8 months.	Bayley MDI, PDI, BRS at 15 months.	Higher PDI (iron-containing micronutrient mix with or without zinc vs riboflavin with or without zinc). Effect size 0·30 SD. Better motor quality and sociability.	Effects presumably due to iron, since other micro-nutrients not linked to behaviour, development, or both.

Table 1: **Double-blind randomised controlled trials of iron supplementation (and other micronutrients) in developing countries**

and B[12] were initially considered but evidence for their effect on development of young children is scarce.[72]

Breastfeeding could benefit development through nutrients in breastmilk, especially essential fatty acids, reduced infant morbidity, or closer mother-child relations.[73] A meta-analysis of 11 studies in developed countries[74] concluded that breastfeeding leads to small cognitive benefits (2–5 IQ points).[73,75] Three reports from developing countries (Chile, Honduras, and the Philippines) on breastfeeding duration and child development were identified, one of which was a randomised controlled trial.[76] These studies showed small improvements in motor development with greater duration of exclusive breastfeeding[76,77] and that early introduction of supplementary bottle feeding was associated with poorer motor and cognitive function.[78] Somewhat larger benefits were reported for babies with low birthweight in one study,[77] including benefits to mental development. Study limitations include lack of randomisation and use of different durations of breastfeeding across studies. However, the findings suggest small benefits to development from breastfeeding.

Zinc deficiency is estimated to affect a third of the world's population, and ranks fifth in the leading risk factors for illness and disease in developing countries.[79] 12 trials with infants have examined zinc supplementation and development. Trials of zinc given alone have shown
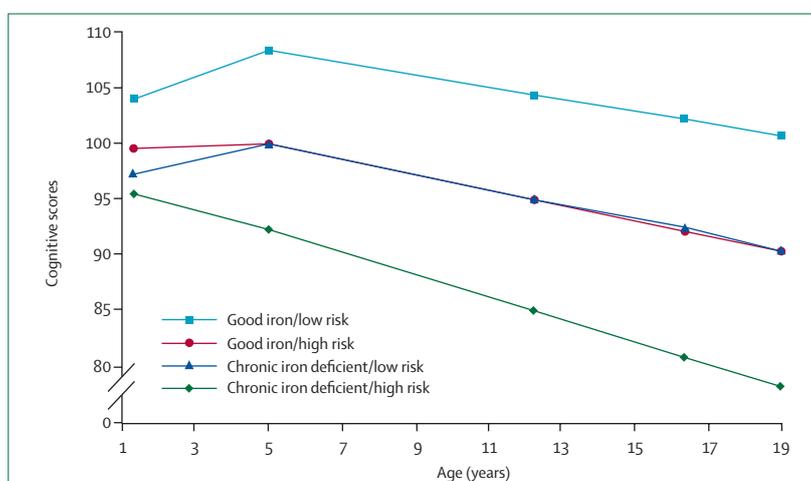
Figure 6: **Cognitive test scores to young adulthood by iron status in infancy and cumulative risk**
In a sample of otherwise healthy full-term Costa Rican infants,[71] longitudinal analysis (hierarchical linear modelling) was used to examine the independent effects and interaction between iron status in infancy and environmental disadvantage on initial cognitive scores (intercept), change from infancy to 5 years (slope 1), and change from 5 years to 19 years (slope 2). Chronic iron deficiency in infancy and increased environmental disadvantage had independent adverse effects on initial scores (p=0.008 and 0.002, respectively). Iron status interacted with environmental disadvantage for both slopes of change over time (p=0.03 and <0.001 for slopes 1 and 2, respectively). There was a significantly different change in cognitive scores for the group of individuals with chronic iron deficiency in infancy and increased environmental risk, compared with all others. Chronic iron deficiency=moderate iron deficiency anaemia at 12–23 months (haemoglobin ≤ 100 g/L) or iron deficiency with a higher haemoglobin and biochemical indicators not fully corrected with 3 months of iron therapy. Good iron status=non-anaemic iron sufficient at study entry, after treatment, or both. High-risk environment=two or more risk factors (mother with low IQ or evidence of depression, less stimulating home environment, or lower socioeconomic status). Low-risk environment=none or one risk factor.

inconsistent findings, possibly because in some studies the children might not have been zinc deficient, other nutrient deficiencies affected development, or because zinc produced imbalances in other micronutrients. Zinc with iron improved motor development and behaviour in one study in Bangladesh,[66] but not in studies from India[80] or Indonesia.[67] Zinc supplementation combined with psychosocial stimulation benefited cognitive and motor development in Jamaica.[81] The effect of zinc deficiency on child development therefore remains unclear. Additional problems such as iron deficiency or poor environments might need simultaneous improvement before benefits of zinc supplementation are seen.

Infectious diseases

Infectious diseases are widespread among children under 5 years in developing countries and can affect development through direct and indirect pathways.[82] Organisms invading the brain parenchyma during a CNS infection or secondary pathophysiological events could cause focal or global damage, leading to neurological impairment. Indirect pathways include effects on nutritional status and decreased physical activity and play. We review those infectious diseases where there is evidence of an association with child development. Other diseases such as meningitis and otitis media might also affect development, but most studies have been done in developed countries.[82]

A third of the world's population is infected with at least one species of intestinal helminth, with the highest prevalence and intensity of infections in school-aged children.[83] There are few studies of the effect of helminths on development in children under 5 years. In the only correlational study identified, presence of intestinal parasites was associated with poor language perfor-mance.[84] Treatment of children with trichuris dysentery syndrome led to benefits to motor development and some improvement in mental development after 4 years.[85] A randomised treatment trial showed no significant effects on language and motor milestones.[68] However, the treatment did not significantly reduce the number and severity of some helminth infections. The limited evidence emphasises the need for further research in this area.

At least 2 million children younger than 14 years are estimated to be living with HIV/AIDS.[9] Infection in infancy can lead to severe encephalopathy with catastrophic outcomes. Even in children without severe outcomes there is increased risk of delays in several developmental domains, especially language acquisition.[9,86] For the much greater numbers of children whose caregivers are HIV-infected, the effects on child development are mediated through reduced resources and psychosocial factors,[9] some of which are reviewed in this paper.

Millions of people live without access to clean water or adequate sanitation,[87] which puts them at high risk for diarrhoeal diseases. Diarrhoea is particularly prevalent during the first 2 years of life.[87,88] Two small Brazilian studies suggest an association between incidence of diarrhoea in the first 2 years of life and impaired cognitive performance in later childhood.[89,90] However, a larger cohort study in Peru with control for confounders saw no independent association with IQ at 9 years of age.[23] Intervention studies are needed to clarify the association between diarrhoeal diseases and child development.

More than 40% of the world's population, in 90 countries, lives with the risk of malaria, with the overwhelming burden affecting children under 5 years in sub-Saharan Africa. There are 300–660 million clinical episodes of malaria every year,[91] and severe malaria accounts for up to 40% of paediatric admissions in parts of sub-Saharan Africa.[92] Neurological and cognitive impairments associated with severe or cerebral malaria have been reported in numerous studies.[93–96] Methodological limitations include differences in case definitions and in criteria for impairment. However, greater degree and duration of impairment has consistently been associated with increased severity of disease.[97] Impairment might also be associated with repeated uncomplicated attacks,[98] potentially affecting millions of children.

Environmental exposures

Environmental exposures are often chronic (eg, contaminated drinking water), therefore in this section we include some studies of older children. Worldwide prevalence of raised lead levels in children are estimated to be around 40%, with children in developing countries being at greater risk of exposure to environmental lead than those in developed countries.[99] In both developing and developed nations, lead exposure is associated with small decrements in IQ (2–5 points) that persist after adjustment for social confounders.[100] In a longitudinal study of children living near a lead smelter in Kosovo, modest deficits in intellectual, motor, visual-motor, and behavioural development appeared from age 2–10 years, even adjusting for social confounders.[101]

At least 30 million people in southeast Asia use water from wells that exceed standards for arsenic.[102] Arsenic exposure, via drinking water or industry, has a known cognitive effect in adults. School-aged Bangladeshi children who drank water contaminated with arsenic showed dose-response decrements in IQ that persisted after adjustment for socio-demographic factors.[103] Similar results were reported for Mexican children[104] and Taiwanese adolescents.[105]

In Bangladesh, school-aged children with drinking water high in manganese had lower IQ scores than children not exposed to high levels of manganese.[106] Compared with those with exposures below 300 ug/dL, those with higher exposures showed a decrement of around 0.3 SD scores. Dose-response relations persisted after socio-demographic adjustment. Similar findings were reported for 11–13-year-old Chinese children.[107]

	Sample	Intervention procedure	Outcome measures	Covariates	Results	Comments
Jamaica.[33] Randomised intervention.	129 stunted children, 9–24 months of age, assigned to 24 months nutrition supplementation, stimulation, both combined, or controls.	Mothers taught educational play techniques and child given educational toys.	DQ assessed by Griffiths Mental Development Test.	Child age, sex, initial DQ, anthropometry, maternal age and IQ, home stimulation, and housing quality.	Control DQs declined and then stabilised; stimulation group DQs increased. Highest DQs in combined stimulation-supplementation group. Effect size differences greater than 1 SD.	Results for supplementation group similar to those of the stimulation group.
South Africa.[118] Randomised intervention.	90 4-year-old children, low socioeconomic families, assigned to 10-week home intervention or to one of two control groups.	Verbal stimulation techniques shown to mother.	Cattell Culture Fair intelligence test used to assess IQ. Observers coded mother-child interaction and child behaviour.	None specified.	Only the intervention group showed gains in cognition, task orientation, positive social behaviour, and reduced distractibility. All group differences remained at 1 year follow-up.	Did not present data on level of group differences.
China.[115] Randomised intervention.	103 preterm infants assigned to 2-year stimulation or to conventional care condition.	Mothers trained to develop child verbal and motor skills. Educational toys provided.	Test of mental and motor development standardised in China.	No differences in family demographics or child biomedical status.	Mental development score of intervention group higher then controls at 18 and 24 months of age (effect sizes greater than 1 SD).	No details given on developmental test.
Turkey.[117] Randomised group intervention.	255 low socioeconomic children aged 3 or 5 years who attended educational or custodial day care centres or no day care. Mothers of children from each group assigned to either 2 years intervention or no intervention.	Mothers trained to promote child language, discrimination, and problem solving skills. Mothers attended group meetings to enhance parenting, coping, and communication skills.	Standardised tests of intelligence, emotional adjustment, and academic skills. Child aggression, dependency, and self-concept assessed. At 6-year follow-up assessed verbal ability, grades, and social-emotional adjustment.	1-year child cognitive performance. In follow-up controlled for prior IQ.	Higher intelligence, academic skills, self-concept, and reduced aggression for intervention group. At 6-year follow-up 86% of children from intervention group still in school compared with 67% non-intervention group. Children in intervention group had higher school grades and greater self-confidence.	No group differences between those children who stayed in the project and those who dropped out during the intervention. No differences in end of intervention scores between those tested in follow-up and those not located. Initial beneficial effects of child being in an educationally oriented preschool disappear if mothers do not receive training also.
Jamaica.[14] Randomised control trial.	140 low-birthweight term low socioeconomic infants assigned to 8-weeks intervention or to control group.	Mothers trained in verbal stimulation, increasing responsiveness, and focusing infant's attention.	Tests of object permanence and means-end. Examiners rated infant behaviour during testing.	Gestational age, mother verbal IQ, and home crowding.	Intervention group had significantly higher performance on the object permanence task and were rated as significantly higher in cooperation and positive emotionality.	Control group also visited weekly to control for attention, but no stimulation offered.
Brazil.[116] Experimental intervention.	156 low socioeconomic infants aged 13–17 months assigned to intervention or control group based on residence area.	Mothers taught to make toys and engage in activities to promote child development.	Children tested at 12 and 18 months using the Bayley Scales of Infant Development (BSID).	No initial group differences on child anthropometry, iron status, level of home stimulation, or initial BSID.	At 18 months intervention group had higher BSID mental (by 9·4 points) and motor scores (by 8·2 points) than controls. Differences stronger for infants with initial BSID scores below 100 (effect size 0·55 SD for infants with BSID greater than 100; 1 SD for infants with BSID less than 100)	
Vietnam.[119] Experimental intervention.	313 children aged 4–5 years from two rural communes. Each had a preschool programme which differed on level of quality. In both communes a 1 year food supplementation programme instituted	A 2-year programme to enhance preschool-teacher training and parent rearing skills was instituted in the commune with the low quality preschool.	Raven's Colored Progressive Matrices (RCPM) given when children were in first and second grade.	Child age, number of children per household, and maternal education. No group differences in anthropometry.	Significantly higher RCPM scores in supplementation plus education intervention commune (effect size 0·09 SD). Intervention effects stronger for stunted (0·61 SD) than non-stunted children (0·06 SD).	RCPM not given before intervention started.

Table 2: Causal studies on the effects of cognitive stimulation interventions

Although worldwide data are not available, water from 6% of wells in the USA exceed the standards of the Environmental Protection Agency for manganese.[108]

More limited or contradictory evidence, relative to what is known from developed nations, exists for other exposures. In an ecologic study of 9–13 year olds in India,[109] prenatal pesticide exposure was associated with lower analytic and memory skill. In a well-controlled Seychelles Islands study there was no effect of prenatal or postnatal methyl-mercury exposure,[110] although

consistent negative associations have been reported in developed nations.[111] One important limitation of some of the studies reviewed is the use of ecologic designs that do not measure individual exposure.[105,107,109]

Psychosocial risk factors

Research from developed countries has identified three aspects of parenting that are consistently related to young children's cognitive and social-emotional competence: cognitive stimulation, caregiver sensitivity and responsiveness to the child, and caregiver affect (emotional warmth or rejection of child).[112] The effect of these factors is sensitive to contextual factors such as poverty, cultural values and practices.[3] Nonetheless, these child-rearing dimensions affect children from developed and developing countries in similar ways.[113,114] Because almost all of the published research from developing countries has involved cognitive stimulation and sensitivity and responsiveness, we do not review caregiver affect. In addition to parenting, we also review two contextual risk factors—maternal depression and exposure to violence.

Parenting Factors
Cognitive stimulation or child learning opportunities
16 experimental or intervention studies assessed the effect of cognitive stimulation on young children from developing countries, including children living in poverty, orphans, and children at biomedical risk. Seven studies selected to provide breadth of geographic region and the type of risk children encountered are listed in table 2.[14,33,115–119]

The remaining studies are summarised in webtable 3. All studies cited in table 2 and all but one cited in the webtable reported significantly higher cognitive functioning in young children given additional cognitive stimulation or learning opportunities than non-stimulated controls. Most effect sizes ranged from 0·5 SD to 1·0 SD. Follow-up studies consistently report lasting effects of early cognitive intervention,[117,118] with some gains maintained for as long as 17 years (figure 4).[26] This pattern of evidence strongly supports the importance of early cognitive stimulation for facilitating young children's cognitive abilities.

Five intervention studies from Jamaica, South Africa, and Turkey assessed non-cognitive outcomes, including three described in table 2[14,117,118] and two summarised in webtable 3. Four of the five studies reported beneficial effects of cognitive stimulation on child task orientation, social behaviour, self-confidence, and positive affect. One limitation is that many of the cognitive stimulation studies also attempted to improve maternal sensitivity and responsiveness. This situation makes it difficult to attribute benefits specifically to cognitive stimulation.

Caregiver sensitivity and responsivity
In studies from Chile, Colombia, India, and South Africa, maternal sensitivity was associated with more secure infant attachment,[120–122] and higher levels of maternal responsivity were associated with higher infant cognitive ability[123] and reduced levels of behaviour problems in preschool children.[124] Intervention studies from Brazil[125] and South Africa[126] that promoted maternal sensitivity and responsivity through providing information to mothers about the capabilities of their young infants showed short-term improvements in maternal behaviour.

Contextual risk factors
Maternal Depression
Prevalence rates for maternal depressive symptoms across developed and developing countries range from 3% to 60%, with rates significantly higher in developing countries[127] (eg, 34.7% of low-income South African mothers were diagnosed with major depression[128]). Consistent with findings from developed countries,[129] reduced levels of cognitive function and higher levels of behaviour problems are reported in young children of depressed mothers from South Africa,[124] Barbados,[130] and India.[131] From the studies cited above, we can not establish whether the consequences of having a depressed mother are due to genetic or environmental factors. However, maternal depression can affect maternal child rearing behaviours.[132] For example in South Africa, depressed mothers were less involved, less sensitive, and more negative when interacting with their infants.[128] Possible treatment approaches for depressed mothers from developing countries are noted in the final paper in this series.

Exposure to violence
Large numbers of children from developing countries are exposed to war or to community and political-sectarian violence.[9] Most studies documenting the effect of direct exposure to armed conflict or the consequences of exposure, such as refugee status and loss of family members, involve children older than 5 years.[8,133,134]

There are few studies from developing countries on the effect on infants and preschool children of exposure to armed conflict or community violence. Studies of young South African children who were exposed to community violence document higher levels of post-traumatic stress disorder,[135] aggression,[136] attention problems, and depression.[137] Similar findings have been reported for young children from a more developed country (Israel) exposed to missile attacks and displacement from their homes.[138]

The negative effect of exposure to violence is likely to be increased when family cohesion or the mental health of primary caregivers is disrupted.[8,133,134] Studies in Eritrea and Bosnia indicate that providing structured educational experiences to war exposed refugee children,[139] or providing parenting training to mothers of such children,[140] can improve children's levels of cognitive and social-emotional competence. In view of the number of children exposed to violence, there is a crucial need for intervention studies with younger children.

	Prevalence in developing countries	Summary of evidence	Estimated effect size
Inadequate cognitive stimulation	Only 10–41% of parents provide cognitively stimulating materials to their child. Only 11–33% of parents actively involve their children in cognitively stimulating activities.	Consistent evidence from intervention studies that providing increased cognitive stimulation or learning opportunities to young children significantly increases both cognitive and social-emotional competence. Long-term gains documented long after the intervention ended.	Benefits from interventions to provide stimulation or learning opportunities: 0·5–1 SD.
Linear growth retardation (an indicator of chronic undernutrition)	31% of children under 5 years of age.	Prospective cohort studies consistently show stunted children have poorer cognitive outcomes and some report social-emotional problems. Supplementation trials all show concurrent benefits, long-term benefits less consistent, most likely in preventive trials.	Severe (<–3SD) compared with non-stunted (>–2SD) : 0·16 SD. Severe (<–3SD) compared with moderate or non-stunted (>–3SD): 0·8 SD. Moderate and severe (<–2 SD compared with non-stunted (>–1 SD): 0·45–0·7 SD.
Iodine deficiency	35% (mild to severe deficiency).	Iodine deficient groups consistently shown to have lower development. Maternal supplementation trials are sufficiently robust to establish that iodine deficiency in utero causes congenital hyperthyroidism and poor development in childhood.	Meta analyses comparing those from iodine deficient areas with iodine sufficient: 0·8–0·9 SD.
Iron deficiency anaemia	23–33% of children 0–4 years.	Iron deficiency anaemia in infancy is associated with short and long-term developmental deficits. Supplementation trials show benefits to motor and social-emotional development. Cognitive benefits reported in trials with preschool children.	Comparing infants with iron deficiency anaemia and non-iron deficient infants: 0·5-1·3 SD.
Malaria	300–660 million clinical episodes per year. Severe malaria accounts for up to 40% of paediatric admissions in sub-Saharan Africa.	Persisting neurological, behavioural, and cognitive impairments are associated with severe malaria, especially cerebral malaria and some evidence of the effect of uncomplicated attacks on development and schooling.	Severe (including cerebral) malaria associated with persisting impairments in up to 24% of childhood survivors.
Maternal depressive symptoms	17% average prevalence rate across countries; rates higher in developing countries.	Consistent evidence from associational studies showing significantly lower cognitive and social-emotional competence in infants of depressed mothers.	Comparing children of mothers with depressive symptoms with those with non-depressed mothers: 0·4–1 SD.
Violence	Major armed conflict in 27–38% of developing countries between 1990–2003, directly affecting as many as 20 million children.	Few studies available on younger children, but available evidence consistently shows impaired cognitive and social-emotional problems in young children.	Depending on outcome and type of violence, 8–34% of negative outcomes associated with exposure to violence; 33% increase in post-traumatic stress disorder in children from more violent communities compared with children from less violent communities.
Low-birthweight infants with intrauterine growth restriction	11% of births.	Cohort studies indicate developmental deficits up to age 3 years. Later deficits are reported from developed countries but only one study at older ages from a developing country.	Compared with normal birthweight (>2500 g): 0·23–0·55 SD. Compared with birthweight 3000–3499 g: 0·57 SD.
Exposure to metals (lead, arsenic)	Around 40% of children have raised lead levels (>10 ug/dL). At least 30 million people in southeast Asia use well water which exceeds arsenic standards.	Lead: studies in a range of settings consistently show small deficit after adjustment for social confounders. Arsenic: small consistent deficits appear even with adjustment for social confounders.	As blood levels increase from 0 to 10 ug/dL: 0·25 SD. Doubling of water arsenic levels: 0·15 SD.

* In the absence of suitable meta-analyses (except for iodine), these are estimates comparing affected and unaffected children in developing countries from those studies where they were provided or it was possible to derive an average effect size. Effect sizes reported are those adjusting for social confounders. Effect sizes 0·5–0·8 are considered moderate, those greater than 0·8 are considered large.[141,142] Prevalence data taken from references cited in the text.

Table 3: Developmental risk factors with sufficient evidence to recommend intervention (prevalence, summary of evidence, and estimated effect sizes)*

Developmental risk factors

In table 3 we present those risk factors where the existing evidence is strong enough to recommend implementation of strategies to reduce or prevent the effect of these risks on young children's development. We base our conclusions on the consistency of the evidence, the numbers of children affected, and the size of the effect on development. The first four risk factors in table 3 each affect at least 20–25% of children in developing countries, and the evidence for their effect on development includes randomised controlled trials. These four factors—inadequate cognitive stimulation, stunting, iron

deficiency, and iodine deficiency—represent crucial risks which are preventing millions of children from reaching their developmental potential, and for which interventions are urgently needed.

The remaining risk factors identified in table 3 also affect substantial numbers of children and have consistent epidemiological evidence that shows their effect on development. Interventions to address these risks are also needed, and their priority will depend on the country context. For example, arsenic is of particular concern in southeast Asia and the prevalence of violence varies considerably between countries.

Although listed separately in table 3, in reality these risks could co-occur. The cumulative risks to which many children are exposed strongly suggest the need for integrated interventions. There are a few examples of successful intervention strategies that targeted multiple risks such as stimulation and nutrient deficiency.[21,33,81,141] Implementation and assessment of other integrated intervention strategies are a high priority.

Research implications

The evidence for the developmental consequences of the risks listed in table 3 is substantial, although questions remain. Future research should investigate mechanisms, the importance of timing, duration, and severity of exposure, and reversibility of effects. Additionally, most of the research concerns the effect on developmental levels in early childhood and on later cognitive outcomes, and most of the effect sizes shown in table 3 relate to cognitive deficits. However social-emotional functioning could be as important to success in school and in adult life.[5] Future research needs to include greater recognition of all aspects of development, with inclusion of social-emotional outcomes.

Other potential risk factors reviewed warrant further investigation. Examples of research needed to establish the importance of these risk factors for child development are given in table 4. We recognise that compelling reasons for interventions to reduce some of these risks already exist (eg, insufficient duration of breastfeeding, diarrhoeal disease). However, evidence for direct links to child development is not yet robust.

	Research needed
Insufficient duration of breastfeeding	Studies in developing countries with sufficient power and which address confounding issues (which differ from those in developed countries). Might be possible to link with ongoing studies of breastfeeding and growth.
Zinc	Randomised controlled trials which address issues raised by existing studies, such as other micronutrient deficiencies, and establishing that children were initially zinc deficient.
Multiple micronutrient deficiency	Multiple micronutrient deficiencies are common, and the effect of multiple micronutrients on child development needs investigation. However, studies of combined iron and zinc suggest that increased benefits cannot be assumed.
Perinatal iron deficiency	A potentially important issue which has received little attention to date. Associational studies on the short-term and long-term developmental consequences of differences in perinatal iron status needed.
Helminth infections	Large-scale studies are needed in younger children with control or adjustment for socioeconomic status and which avoid treatment issues encountered in studies of schoolchildren (eg, short treatment regimens that might not reverse the cumulative effect of chronic infections).
Diarrhoeal disease	Well-controlled intervention studies, perhaps targeting water sources and sanitation, are needed to better understand the association between diarrhoeal diseases in early childhood and impaired child development.
Pesticides	Investigation of the effect of increasing use of agricultural pesticides on the development of young children.
Caregiver responsivity	Intervention studies designed to show if gains in maternal sensitive responsiveness result in higher cognitive and social competence in their offspring.
Caregiver affect	Intervention studies to determine if increasing maternal positive emotional involvement with her infant can promote more secure infant attachment.

Table 4: **Research questions for less well-established developmental risk factors**

Conclusions

Currently available evidence shows that specific risks encountered by young children in developing countries compromise their development. The numbers of children affected are enormous; in some countries 40–50% of children under 5 years are stunted. The risks described in this paper, all of which are modifiable, prevent millions of children from benefiting fully from the educational opportunities to which they have access. Education is vital for both individuals and nations to emerge from poverty. Crucially, we need to move forward with interventions and policies designed to prevent this loss of human potential. Intervention strategies will be addressed in the final paper in this series.

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