Child Development 1

Inequality in early childhood: risk and protective factors for early child development


Inequality between and within populations has origins in adverse early experiences. Developmental neuroscience shows how early biological and psychosocial experiences affect brain development. We previously identified inadequate cognitive stimulation, stunting, iodine deficiency, and iron-deficiency anaemia as key risks that prevent millions of young children from attaining their developmental potential. Recent research emphasises the importance of these risks, strengthens the evidence for other risk factors including intrauterine growth restriction, malaria, lead exposure, HIV infection, maternal depression, institutionalisation, and exposure to societal violence, and identifies protective factors such as breastfeeding and maternal education. Evidence on risks resulting from prenatal maternal nutrition, maternal stress, and families affected with HIV is emerging. Interventions are urgently needed to reduce children’s risk exposure and to promote development in affected children. Our goal is to provide information to help the setting of priorities for early child development programmes and policies to benefit the world’s poorest children and reduce persistent inequalities.

Introduction

In a 2007 Series in The Lancet we estimated that more than 200 million children younger than 5 years from low-income and middle-income countries were not attaining their developmental potential, primarily because of poverty, nutritional deficiencies, and inadequate learning opportunities. Economic recession and climate change will probably increase the number of children affected. Biological and psychosocial risk factors associated with poverty lead to inequalities in early child development, which undermine educational attainment and adult productivity, thereby perpetuating the poverty cycle. In this Series, we review new evidence on the mechanisms and causes of developmental inequality and economic implications and strategies to promote early child development. In this report we summarise evidence from developmental neuroscience on how experiences in early life affect the structure and functioning of the brain, and subsequent child development. We review evidence on risks and protective factors for development, updating evidence on previously identified risks (panel 1), and highlight risks not previously identified.

Our focus is on modifiable risks that affect large numbers of children younger than 5 years in low-income and middle-income countries.

Key messages

- Exposure to biological and psychosocial risks affects the developing brain and compromises the development of children.
- Inequalities in child development begin prenatally and in the first years of life.
- With cumulative exposure to developmental risks, disparities widen and trajectories become more firmly established.
- Reducing inequalities requires early integrated interventions that target the many risks to which children in a particular setting are exposed.
- The most effective and cost-efficient time to prevent inequalities is early in life before trajectories have been firmly established.
- Action or lack of action will have lifetime consequences for adult functioning, for the care of the next generation, and for the wellbeing of societies.

Search strategy and selection criteria

We searched relevant databases (eg, PubMed, PsychInfo, Cochrane Review) with multiple search terms for articles published since 2005. The search terms we used were linked to each of the risk or protective factors: “child development”, “child behaviour”, “infant behaviour”, “cognition”, “social”, “emotional”, “intelligence”, “language”, and “motor development”. We searched citation lists of articles retrieved and review articles published since the last Series for further references. We included earlier key publications in which the risk or protective factor was not reviewed in the previous Series. We include only risk and protective factors that can be modified by interventions or public policy and which affect large numbers of children younger than 5 years in low-income and middle-income countries. We consider exposures in utero to age 5 years and focus on research done in low-income and middle-income countries. Although many of the risk and protective factors we considered are also relevant to children’s health outcomes, we focus on children’s cognitive, motor, and social-emotional development.
Risk, stress, and brain development
The foundations of brain architecture are laid down early in life through dynamic interactions of genetic, biological, and psychosocial influences, and child behaviour. Biological and psychosocial influences affect the timing and pattern of genetic expression, which can alter brain structure and function, and behaviour. Through bidirectional effects, children’s behaviour affects brain development directly and by modifying the effects of biological and psychosocial influences.

Childhood risks associated with poverty, such as lack of stimulation or excessive stress, affect brain development, result in dysregulation of the hypothalamic–pituitary–adrenocortical system, and change electrical activity of the brain related to efficiency of cognitive processing. The influence of risks can begin prenatally because the fetal brain can be influenced by exogenous factors that produce maternal stress. At present there is insufficient evidence from research in human beings to establish if the effects on hypothalamic–pituitary–adrenocortical regulation are reversible.

Three translational processes influence how risk factors and stress affect brain and behavioural development: the extent and nature of deficits depend on timing, co-occurring and cumulative influences, and differential reactivity (figure 1 and table 1). Risks often co-occur and persist, leading to exposure to multiple and cumulative risks. For example, maternal depression increases risk of low birthweight (LBW; additional references in web appendix pp 1–5), stunting, and behaviour. Because of differential reactivity, the effect of risks on behaviour might vary by individual or environmental characteristics.

Maternal nutrition
There is maternal undernutrition (body-mass index <18.5 kg/m²) in 10–19% of women in most low-income and middle-income countries, with higher prevalence in sub-Saharan Africa and south Asia. Maternal pre-pregnancy body-mass index and weight gain during pregnancy predict birthweight, and balanced energy–protein supplementation benefits birthweight and reduces births that are small for their gestational age. However, there is little information on associations between maternal nutritional status and child development. Pre-pregnancy weight and weight gain in Jamaican women that were mostly adequately nourished were not associated with child cognition at age 7 years. In Bangladesh, infants of undernourished mothers had poorer problem-solving ability at 7 months, and ability was better in infants of mothers given food supplements early rather than later in pregnancy. By age 18 months, no effects of maternal undernutrition or supplementation were identified.

Analyses of the Dutch (1944–45) and Chinese (1959–61) famines suggest that prenatal nutritional deficits might have long-term effects on adult mental health. There is a need for research on the effect of food supplementation before and during pregnancy on child development.

About 42% of pregnant women in low-income and middle-income countries are anaemic, and, of these, 60% are iron deficient; however, there is little information on perinatal iron deficiency and child development. Lower maternal haemoglobin and neonatal ferritin predicted lower intra-individual variability in temperament-like behaviours in Peruvian infants that suggested diminished responsiveness. In South Africa, maternal iron-deficiency anaemia at 6–10 weeks post partum was associated with lower maternal sensitivity and child responsiveness. Although both disorders improved after treatment with iron, infant development was delayed at age 9 months.

Meta-analyses of 12 randomised controlled trials from low-income and middle-income countries show that supplementation with multiple micronutrients in pregnancy leads to increased birthweight. Trials of supplementation with multiple micronutrients during pregnancy in Bangladesh and in pregnant women in Tanzania infected with HIV suggest small benefits to infants’ motor development, and to mental development in China, compared with iron and folic acid alone. In Peru, zinc supplementation during pregnancy had no effect on children’s cognitive, social, or behavioural development at ages 4–5 years. In Nepal, children whose mothers received iron and folic acid during pregnancy had better intelligence quotient (IQ), executive, and motor functioning than the placebo group at ages 7–9 years; provision of multiple micronutrients or iron plus folic acid plus zinc had no benefits, possibly because of zinc inhibition of iron absorption.

Inadequate intakes of ω3 fatty acids (including α-linoleic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid) have been reported in pregnant women in some low-income and middle-income countries. In high-income countries, trials of fish oil, DHA, or DHA and eicosapentaenoic acid showed that infants born to supplemented mothers had improvements in visual acuity, attention, and aspects of cognitive performance. Supplementation with ω3 fatty acids and micronutrients benefited birthweight and length and reduced very early preterm births in Chile. In Mexico, supplementation with ω3 fatty acids benefited birthweight and head size in primigravid women only. Information is needed on possible benefits to infant development.

Panel 1: Previously identified priority risk factors
- Key risks: inadequate cognitive stimulation, linear growth retardation (stunting), iodine deficiency, and iron-deficiency anaemia
- Other priority risks: intrauterine growth restriction, malaria, lead exposure, maternal depressive symptoms, and exposure to violence
Infant and child nutrition

In low-income and middle-income countries, 16% of births are LBW with rates as great as 27% in south Asia, most of these births being intrauterine growth restriction (IUGR)-LBW. A Guatemalan study showed associations between birth size adjusted for gestational age and development at 6 and 24 months, supporting earlier conclusions that IUGR is associated with early developmental risk.1

Evidence for longer-term effects of IUGR is less consistent. Significant effects of birthweight unadjusted for gestational age were identified on IQ at age 5 years29 and on highest school grade achieved.30 However, contributions of prematurity cannot be estimated. No evidence was found for any association between term LBW and normal birthweight children in IQ or parent–child interactions.31 Studies from Taiwan34 reported significant small deficits in academic achievement of term LBW at 15 years. More evidence is needed on long-term effects of IUGR in low-income and middle-income countries on IQ, and specific cognitive and social skills.

About 39% of infants aged 0–6 months in low-income and middle-income countries are exclusively breastfed, with wide variations in duration of exclusive breastfeeding between countries. In a large cluster-randomised trial in Belarus,35 clinics were assigned to breastfeeding promotion or usual care. Intervention increased exclusive breastfeeding at 3 months and any breastfeeding up to 12 months. At age 6·5 years, intervention children had 0·5–0·8 school grades more for at least 9 months attained 0·5–0·8 school grades more by 18 years than boys breastfed for less than 1 month. Regression of grade level attained on adult income in this population suggests this difference corresponds to a 10–15% difference in income.” These findings strengthen the evidence for benefits of breastfeeding to development and educational attainment.

In high-income countries, formula-fed infants given DHA supplemented formula had better visual acuity, with greater benefits for preterm infants. There is little information on essential fatty-acid intake or the developmental effect in infants and children from low-income and middle-income countries. In Turkey, improvements in brainstem auditory evoked potentials were noted in infants randomly assigned to receive DHA-supplemented formula compared with infants receiving non-supplemented formula.38 Consumption of complementary foods fortified with micronutrients and essential fatty acids was associated with improved motor development in Ghana and China.36,37 Although it is unclear which nutrients were responsible for the benefits, supplementation with essential fatty acids and micronutrients resulted in earlier walking compared with micronutrients alone;37 however, the groups also differed in energy intake.

Linear growth retardation or stunting is estimated to affect 34% of children younger than 5 years in low-income and middle-income countries. Consistent with previous evidence, new longitudinal studies from Brazil, India, Peru, and Vietnam show associations between early height-for-age and cognitive or language ability at 5 years.

Height before 6 years was related to age at school enrolment and grades attained by late adolescence in Zimbabwe.40 New information also extends the long-term outcomes associated with stunting, including reduced likelihood of formal employment at age 20–22 years in the Philippines42 and poorer psychological functioning in Jamaican adolescents.43

Timing of growth faltering seems important. In Guatemala, growth and development were related up to age 24 months but not from 24 to 36 months.39 Pooled analyses of five longitudinal studies identified that a 1 SD increase in weight gain from birth to 24 months was associated with increased schooling (0–43 years) and inversely related to grade failures, whereas growth from

Figure 1: Pathways linking poverty to developmental inequities

(A) Timing, dose, and differential reactivity influence how individual exposure to risk and protective factors translate into individual differences in brain function and structure. (B) Brain structure and function influence the degree of differential reactivity shown. (C) Timing and dose of exposure, and differential reactivity moderate the effect of risk and protective factors upon child development.

Table 1: Translational processes underlying the effect of risk exposure on brain and behavioural development

<table>
<thead>
<tr>
<th>Example(s)</th>
<th>Translational processes: timing, dose, differential reactivity</th>
<th>Risks</th>
<th>Protective factors</th>
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<tr>
<td>The infant–caregiver relationship depends on the quality and availability of caregiving early in life, the same period that is sensitive to the effect of iron deficiency on myelination and density of dopamine receptors</td>
<td>Timing: extrinsic and environmental influences have maximum effect on brain and behavioural development during specific ages (sensitive periods)</td>
<td>CNS, neurotransmitters, stress-linked autonomic and hormonal endocrine systems</td>
<td>Family poverty</td>
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<td>When stress is cumulative or severe, the risk of adverse long-term physiological and behavioural consequences is substantially increased; early cumulative exposure to stress might compromise children’s ability to benefit from supportive environments, or increase their susceptibility to later stressors</td>
<td>Co-occurring or cumulative influences (dose): risk and protective factors that cumulate during a sensitive period or over time are potent adverse (risk) or facilitative (protective) influences on biological and behavioural development</td>
<td>Protective factors</td>
<td></td>
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2 to 4 years had little affect. Duration might also change the effect because Peruvian children stunted at age 6–18 months, but not at 4·5–6 years, did not differ from children who were not stunted at either age in vocabulary and quantitative test scores at 4·5–6 years. Children stunted at both ages had significantly lower scores. The timing of catch-up growth is unknown and might have happened within the first 2 years of life.44

Previous randomised controlled trials of macronutrient supplementation to promote better growth consistently showed concurrent developmental benefits.1 Follow-up of a cluster-randomised trial in Guatemala showed benefits to reading comprehension and reasoning at 25–42 years in participants supplemented from birth to 24 months, but not those supplemented later.45 Men supplemented throughout the first 3 years earned higher hourly wages.46 These findings highlight the importance of adequate nutrition early in life.

Several studies reported previously unrecognised behavioural or neurophysiological alterations with iron-deficiency anaemia in infancy (webappendix pp 9–28). Studies in Chile, India, and Mexico identified electrophysiological evidence of delayed brain maturation in infants with iron-deficiency anaemia. Sleep duration improved with iron plus folic acid or zinc supplementation, but not both, in trials in Zanzibar and Nepal.4 However, sleep-state organisation was altered in Chilean children aged 4 years despite treatment for iron-deficiency anaemia in infancy.46 Additional evidence from studies in Chile, India, Mexico, and Zanzibar showed poorer cognitive, motor, and social–emotional development associated with iron-deficiency anaemia in infancy, or the preschool period. Social–emotional development improved in Chilean infants with iron-deficiency anaemia who received home visitation to promote development, but remained lower than that of non-anaemic infants. Without home visitation social–emotional development declined in infants with iron-deficiency anaemia.49

Costa Rican adolescents who had chronic, severe iron deficiency with or without anaemia in infancy showed no catch-up in motor development despite iron therapy in infancy,10 poorer executive functioning and recognition memory at age 19 years,11 and more internalising and externalising behaviour problems in childhood and adolescence.12 A study of fortification of complementary feeding in China noted infants whose anaemia did not correct within 6 months had lower IQ at age 6 years than those whose anaemia resolved.13

In addition to iron, many other micronutrients are deficient in children in low-income and middle-income countries including zinc, vitamins A, B12, D, E, riboflavin, and iodine in some regions. Six randomised and one non-randomised trial of supplementation with multiple micronutrients or fortification included three or more micronutrients and assessed development in children younger than 5 years (webappendix pp 29–37). Five of seven studies showed benefits to motor development. Studies from Bangladesh and India assessing mental development did not identify any benefits,14,15 and one from China identified small benefits for mental development at 24 months and for IQ at 6 years.49 There are insufficient data to establish whether supplementation with multiple micronutrients is more effective than iron alone in improving development.

Infectious diseases

Previous evidence of the effect of diarrhoea on child development was inconclusive. Additional studies in Brazil noted associations between the number of diarrhoea episodes before age 2 years, late school entry,55 deficits in semantic fluency, and verbal learning,56 adjusting for socioeconomic status and present nutritional status. Adjustment for stunting before age 2 attenuates the association between diarrhoea and intellectual performance.57 A multicountry study showed that each episode of diarrhoea in the first 2 years of life contributes to stunting,58 suggesting that associations between diarrhoea early in life and school-age performance might be through the same processes that cause stunting.

1·2 billion people are at risk of malaria, with children younger than 5 years at greatest risk. Cerebral or severe malaria can have serious neurological sequelae including seizures, and language and cognitive deficits.1,59 In Uganda, cognitive training interventions improved the function of affected children.59

New evidence suggests that repeated uncomplicated attacks and asymptomatic parasitaemia (experienced by millions of children annually) also affect children’s development. In a cross-country analysis controlling for education quality and other confounders, grade repetition and primary school completion rates were related to malaria exposure.60 Longitudinal studies with school-aged children from Brazil and Mali have shown associations between attacks of clinical malaria or asymptomatic parasitaemia and poorer cognitive scores and academic performance. Randomised clinical trials of chemoprophylaxis in schoolchildren showed significant benefits to language, mathematics, and attendance in Sri Lanka,61 and to attention in Kenya.62 There are fewer studies with children younger than 5 years. A history of malaria attacks was associated with poorer cognitive function at school entry in Sri Lanka,63 and there were inconsistent associations between parasitaemia and activity and exploration in toddlers in Zanzibar.64 Chemoprophylaxis in young children in The Gambia had later benefits for grades attained64 but not cognitive function, although duration of intervention was related to cognitive function. Although most data come from studies of school-aged children, malaria attacks are more common and severe in younger children, and cognitive effects might be worse. Despite progress in control programmes, in 18 African countries surveyed only 23% of children younger than 5 years and...
27% of pregnant women were sleeping under insecticide-treated nets.

Most studies investigating other parasitic infections and child cognitive or social-emotional performance involve school-age children. The few studies with young children are inconclusive.1 Although one additional study from Brazil29 showed an association between the number of parasitic infections at 1–3 years and lower IQ at 5 years, findings were not significant after covariate control. Evidence is insufficient to establish if early parasitic infections affect child development.

An estimated 2·1 million children younger than 15 years are living with HIV; however, only 28% of children in low-income and middle-income countries who need antiretroviral drugs receive them. HIV infection affects brain development, leading to cognitive impairments.65 Detrimental effects of HIV infection on neurocognitive development were identified in 36 of 43 studies from low-income, middle-income, and high-income countries.66 We summarise in the webappendix (pp 33–37) studies of the development of children younger than 5 years infected with HIV from low-income and middle-income countries. Compared with uninfected children, children infected with HIV had significantly lower motor and mental development scores in most studies. Effects are accentuated by associated illnesses, poor nutritional status, and adverse living conditions, including caregiver stress, illness, and death (co-occurrence or cumulative influences).

In US studies, highly active antiretroviral therapy (HAART) has led to reduced rates of progressive HIV encephalopathy64 and some benefits to development.69 Cognitive function did not change after short-term treatment (6 months) in South African children;60 however, benefits to motor and cognitive development were noted after 1 year in the Democratic Republic of the Congo with greater benefits in younger children.71 There is an urgent need for increased access to treatment for infected children in low-income and middle-income countries and further assessment of the effect of early treatment on development.

Cognitive and motor deficits have been reported in HIV-exposed uninfected children in low-income and middle-income countries including the Democratic Republic of the Congo73 and Thailand.74 However, co-occurring risks such as family poverty and non-parental caregivers were also increased and other studies have not identified deficits (webappendix pp 33–37). Many uninfected children are affected by parental HIV, which can increase exposure to developmental risks such as poverty,73 disrupted caregiving,74 and abandonment.75 In South Africa, young children in affected households with caregiver illness or death were at risk for bullying, mental health problems,75 and abuse,76 and in Rwanda for emotional and behavioural problems.75 The restricted financial and social support available to non-parental caregivers further challenges the wellbeing of orphans.77

Environmental toxins

Children might be exposed to environmental toxins prenatally—through maternal exposure—and postnatally—through breastmilk, food, water, house dust, or soil. We previously identified lead as a risk factor for young children from low-income and middle-income countries.5 Recent evidence from Poland has shown that prenatal exposure to very low concentrations of lead (<5 μg/dL) can result in poor mental development in young children.64 Evidence from low-income and middle-income countries on the effect of other toxins on early child development is inconsistent or sparse (webappendix pp 38–39). Evidence from China shows that arsenic exposure can compromise cognition in older children;86 however, studies from Bangladesh have not identified significant associations between arsenic exposure and mental development up to age 2 years.77 Prenatal exposure to mercury has been linked to low cognitive performance in infancy and early childhood in Brazil,62 but studies from the Seychelles report weak or inconsistent effects,81 or no effects.84 In Ecuador, prenatal exposure to pesticides was significantly associated with poor communication and motor skills;85 however, associations with later development were weaker,85 or non-significant in Mexico.66 Prenatal exposure to polycyclic aromatic hydrocarbons was associated with slower language and cognitive development up to age 2 years in China86 and intelligence at age 5 years in Poland.88

Comparison of findings is difficult because of variability in exposure duration, timing, and outcome measures.65 Inconsistent findings might also relate to differential reactivity, in which effects are modified by risk factors, such as low birthweight or malnutrition.66 Alternatively, the effect of toxins might be reduced when exposure is associated with protective influences, such as polyunsaturated fatty acids in mercury contaminated fish, or better health care for children of mothers employed on farms. Further evidence is needed of the effects of toxins on early child development as well as further assessment of interactions with other exposures.

Disabilities

In a survey of disability in 18 low-income and middle-income countries, 23% of children aged 2–9 years had, or were at risk for, disabilities. Besides being a marker for compromised development, childhood disabilities can reduce access to school or health services, and increase risk of caregiver stress and depression69 (webappendix p 40). Studies from south Asia suggest that learning and social integration is also limited by social stigma86 and overprotection by parents.87

Although interventions can promote better function in children with disabilities, few have been assessed in low-income and middle-income countries. Randomised trials suggest more positive attitudes after interactive group therapy in parents of children with intellectual disabilities.
in India, and benefits from mother–child group intervention or parent training to child development and maternal adaptation for children with cerebral palsy in Bangladesh. Quasieperimental studies of parent-training programmes have shown some benefits to child development and maternal behaviour (webappendix p 40).

Evidence on availability of services is scarce but studies from Pakistan and South Africa report that few children receive adequate services. Identifying barriers to accessing services is an important priority for children with disabilities. Community-based approaches to provision of services are discussed in the second paper in this Series.

**Psychosocial factors**

*Early learning and caregiver–child interaction*

Learning opportunities that facilitate early cognitive development include caregiver activities and materials that promote age-appropriate language and problem-solving skills. Caregiver–child interactions that facilitate early social–emotional development include caregiver positive emotionality, sensitivity, and responsiveness toward the child, and avoidance of harsh physical punishment. Lack of early learning opportunities and appropriate caregiver–child interactions contribute to loss of developmental potential. We review new studies that assess the effect of interventions to increase learning opportunities and improve caregiver–child interaction (table 2 and webappendix pp 41–45). The second paper in the Series discusses the effectiveness of interventions that are, or could be, implemented at scale.

Studies from Bangladesh, China, India, and South Africa have shown that interventions to enhance mother–child interactions and increase developmentally facilitative activities benefit cognitive development when delivered through home visits, individual parent

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<th>Sample and intervention</th>
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<td><strong>Chile</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Children aged 6 and 12 months with iron-deficiency anaemia or who were non-anaemic were randomly assigned to intervention or surveillance groups for 1 year (n=277); infants were given oral iron for 1 year (6-month group) or 6 months (12-month group); surveillance groups received weekly visits to monitor feeding and health, intervention groups received weekly home visits by professional educators to promote development through improving the mother–child relationship</td>
<td>Significant benefit of intervention to cognitive and social-emotional scores of infants with iron-deficiency anaemia.</td>
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<td><strong>South Africa</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Women recruited in late pregnancy from two periurban settlements; randomly assigned to intervention (n=220) or control group (n=229); caregivers were taught through home stimulation programmes individualised to their infant's abilities, 16 visits antenatal to 5 months</td>
<td>Intervention mothers more sensitive and less intrusive at 6 and 12 months (d=0·24–0·26); infants more securely attached at 18 months</td>
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<td><strong>China</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>100 families with a child younger than 2 years from seven randomly selected villages; families randomly allocated to intervention (n=50) or control (n=50) groups; intervention was 20–30 min counselling sessions with the WHO Care for Development guidelines, one on enrolment and one within 6 months; mothers were given a card with age-specific messages; counselling sessions included demonstration of play activities and practice, discussion of obstacles to implementation and problem solving</td>
<td>Significant benefits after 6 months to Gesell quotients in adaptive (d=0·49), language (d=0·52), and social (d=0·17) development; no benefits to motor development</td>
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<td><strong>India</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>800 infants admitted to special-care nursery randomly assigned to intervention or control groups; 27% preterm, 50% LBW, 46% infants tested at 1 year, 73% at 2 years; mothers trained individually and in groups to give stimulation and to continue at home; compliance assessed at monthly home visits, intervention given for 1 year</td>
<td>Benefits to Bayley mental developmental index and psychomotor developmental index scores at 1 year (effect size mental developmental index 0·38, psychomotor developmental index 0·40); effect size at 2 about half that at 1 year; benefits for VLBW, LBW, and NBW infants</td>
</tr>
<tr>
<td><strong>South Africa</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>122 HIV-positive children aged &lt;30 months randomly assigned to intervention or control groups (institutionalised children excluded); caregivers taught through home stimulation programmes individualised for their child at usual clinic visit every 3 months, structured around daily activities and developmentally appropriate play; caregivers given a picture book and asked to spend time with child looking at and talking about pictures daily</td>
<td>Significant improvement after 12 months in intervention group compared with control in Bayley mental developmental index (d=0·27) and psychomotor developmental index (d=0·19)</td>
</tr>
<tr>
<td><strong>Jamaica</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Five inner-city preschools randomly assigned to intervention or control; children aged 2–5 years nominated by their teacher as having a behaviour difficulty were assessed (intervention n=69, control=66); intervention based on Incredible Years teacher training programme (seven full-day teacher workshops and monthly classroom consultations) and 14 child lessons on social and emotional skills in each class; control schools received educational materials only</td>
<td>Intervention children had reduced conduct problems (d=0·26), hyperactivity (d=0·36), and peer problems (d=0·71) by teacher report; no significant benefits to prosocial behaviour or emotional problems</td>
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| Table 2: Effects of early interventions on cognitive and social-emotional development |

<sup>d</sup> effect size, Cohen’s d. LBW=low birthweight. VLBW=very low birthweight. NBW=normal birthweight.
counselling delivered at health centres, or combined approaches. Benefits have been shown in children with risk conditions such as severe malnutrition, LBW, iron-deficiency anaemia, or HIV infection. Group parenting education benefited mental development in one of three studies (webappendix p 41–45).

In Chile and South Africa, early interventions to improve mother–child interaction promoted attachment and social–emotional development, although gains were not identified in Bangladesh. A preschool intervention in Jamaica to promote social–emotional development reduced child-behaviour problems.

Sustained intervention benefits to cognitive function at age 18 years have previously been reported. Studies from Jamaica and Turkey show benefits to college attendance, psychological functioning, and cognition and behaviour at age 6 years.

Maternal depression

A recent study from Bangladesh provides further evidence of the high incidence of maternal depressive symptoms in many low-income and middle-income countries. Maternal depressive symptoms are negatively associated with early child development and quality of parenting across different cultures and socioeconomic groups. In Bangladesh, maternal depressive symptoms were associated with infant stunting, perhaps related to unresponsive caregiving (webappendix p 46). Risk factors for maternal depression, such as poverty, low education, high stress, lack of empowerment, and poor social support are also risk factors for poor child development, suggesting that the relation between maternal depression and compromised early child development is multilevel and cumulative.

Availability of mental health care is restricted in many low-income and middle-income countries. In Pakistan and South Africa, interventions delivered by community health workers have reduced maternal depressive symptoms, and improved maternal sensitivity and infant attachment, infant health, and time spent playing with infants. Evidence that symptoms of maternal depression can be effectively treated in low-income and middle-income countries, often with restricted resources and community health workers, emphasises the need for early identification and community programmes to reduce the risk of adverse consequences for mothers and children.

Table 3: Neural consequences of institutionalisation

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<th>Findings</th>
<th>Clinical implications</th>
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<tr>
<td>Metabolic function</td>
<td>Romanian children institutionalised early in life, adopted, and followed up at mean age of 8.8 years</td>
<td>PET scan revealed significantly reduced brain metabolism in the prefrontal cortex and temporal lobe, compared with non-institutionalised children</td>
</tr>
<tr>
<td>Brain structure</td>
<td>Romanian children institutionalised early in life, adopted, and followed up at adolescence</td>
<td>MRI scans showed significantly reduced grey-matter and white-matter volume and an enlarged amygdala, compared with non-institutionalised children</td>
</tr>
<tr>
<td>Brain neurochemistry</td>
<td>Cohort of internationally adopted children</td>
<td>Children adopted from poor institutional care might exhibit raised cortisol concentrations years after adoption</td>
</tr>
<tr>
<td>Brain electrophysiology</td>
<td>Bucharest Early Intervention Project, a randomised controlled trial of foster care as an intervention for early institutionalisation</td>
<td>Institutionalised children showed reduced amplitude in event related potential components, compared with non-institutionalised children</td>
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Exposure to violence

Estimates suggest that 300 million children younger than 5 years have been exposed to societal violence. New studies further show the adverse consequences of exposure to violence in young children (webappendix p 47). Although domestic violence and child abuse happen in countries of all incomes, we focus here on societal or community violence that might be particularly common in low-income and middle-income countries.

Young children exposed to societal violence show insecure attachments, increased risk of behaviour problems, reduced levels of prosocial behaviour, and increased aggressive behaviour. The adverse consequences might result from disruptions to family structure and function that compromise the adequacy of maternal childrearing skills, and reduce children’s ability to regulate their own emotions.

Studies from Israel and Palestine identified intervention strategies that can reduce stress reactions for young children. The effect of exposure to violence can be reduced by supportive parental reactions and positive family routines; however, violence can disrupt the quality of parenting, thereby reducing families’ ability to protect young children exposed to violence.
At least 2 million children are institutionalised in non-parental-group residential care. This is probably an underestimate because of under-reporting and lack of information for some regions. Use of orphanages and other institutional care seems to be increasing. Although children’s response to institutionalisation varies, many show long-term developmental deficits. Institutional rearing starting early in life increases children’s risk for adverse outcomes including poor growth, ill-health, attachment disorders, attention disorders, poor cognitive function, anxiety, and autistic-like behaviour.

Recent studies of institutionalised children show the effect of early experiences on brain development. Institutional rearing has been associated with reduced metabolism in the temporal and frontal cortices, reductions in white-matter connectivity, reductions in brain electrical activity, dysregulation of the hypothalamic–pituitary–adrenocortical system, and changes in brain volume (particularly the amygdala; table 3 and webappendix p 48). Illustrating the translational processes of timing and cumulative exposure (table 1), children experiencing longer institutional placement show larger reductions in left amygdala volume whereas children adopted from institutions before the second year of life have more normalised amygdala volume and brain electrical activity.

Adverse neural consequences underlie the behavioural sequelae of early institutionalisation.

Improving the institutional environment (eg, training staff in sensitive responsive caregiving; increasing caregiver stability and the caregiver-to-child ratio) results in significant benefits to child cognitive and social–emotional competence.

Protective influences

Protective factors attenuate adverse consequences of risk factors. Although risk and protective factors are conceptually distinct, many protective factors are the inverse of risk factors (eg, insecure attachment vs secure attachment). Studies in high-income countries have identified biological, psychosocial, and behavioural protective factors for young children, but there are few studies from low-income and middle-income countries. The protective effects of breastfeeding and early cognitive and social–emotional stimulation were reviewed in previous sections. Maternal education also can act as a protective factor, reducing child mortality and promoting early child development.

Young children of educated mothers have higher levels of cognitive development than children of less educated mothers. Similarly, high-risk infants and young
children show better developmental trajectories when their mothers have higher levels of education. In panel 2 we show the protective mechanisms linking maternal education and early child development. Children of less-educated mothers are likely to have lower maternal education and early child development. Poorly educated women might benefit less from participation in parent-focused programmes than better-educated women (differential reactivity), emphasising the need for strategies to increase their participation and learning in early child-development interventions.

Conclusions

Major advances in neuroscience show how exposure to biological and psychosocial risk factors, prenatally and during early childhood, affects brain structure and function and compromises children’s development and subsequent developmental trajectory. We summarise in figure 2 how risk and protective factors encountered before age 5 years compromise children’s development. The greater the exposure to cumulative risks the greater is the need for effective strategies.

Table 4

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Recent evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate stimulation and opportunities for learning</td>
<td>Increased evidence of intervention benefits for social–emotional outcomes (ES 0.74-0.79) and further evidence of benefits to cognitive outcomes (ES 0.27-0.85; table 2 and webappendix pp 41-45)</td>
<td>Need for effective strategies for scaling up programmes that promote early stimulation and learning opportunities and integration with health and nutrition services for young children</td>
</tr>
<tr>
<td>Stunting (linear growth retardation)</td>
<td>Evidence of effect on ability at age 5 years (ES 0.2 for stunting at age 1 year) and long-term outcomes such as educational attainment, increased formal employment (ES 0.2 for 1 SD change in height for age at age 2) and psychological functioning (ES 0.4-0.5 comparing stunted and non-stunted)</td>
<td>Results further emphasise the importance of adequate nutrition in the first 2 years; stimulation should be an integral part of intervention for stunted children</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>We did not discuss this in view of previous conclusive findings; for recent supporting studies see webappendix p 51</td>
<td>Need for continued attention to expanding and ensuring quality control of fortification programmes</td>
</tr>
<tr>
<td>Iron-deficiency anaemia</td>
<td>Evidence for neurophysiological changes and neural mechanisms leading to developmental deficits; ES medium to large; increased evidence of long-term cognitive and behavioural effects of early iron-deficiency anaemia; ES small to large (webappendix pp 9-28)</td>
<td>Results emphasise the importance of prevention of iron deficiency early in life</td>
</tr>
<tr>
<td>IUGR</td>
<td>Consistent evidence for lower developmental levels in early childhood; evidence for long-term effects mixed (ES 0.19-0.14)</td>
<td>IUGR infants likely to benefit from early interventions to promote development; need for increased strategies to reduce IUGR including better maternal nutrition</td>
</tr>
<tr>
<td>Malaria</td>
<td>Increased evidence for long-term deficits due to cerebral and severe malaria; less information for children younger than 5 years but longitudinal studies suggest uncomplicated attacks are associated with reduced ability at school entry (reading and language one to four attacks ES 0.77-0.47; greater than four attacks 0.57-0.92) and fewer attacks with better subsequent educational achievement (ES 0.22-0.62)</td>
<td>Need for expansion of prevention programmes (eg, insecticide-treated bednets)</td>
</tr>
<tr>
<td>Lead exposure</td>
<td>Evidence for adverse effects of low concentrations of prenatal exposure for child development (ES 0.19-0.27)</td>
<td>Continued attention to prevention of exposure to lead (eg, through removal of lead in paint, gasoline)</td>
</tr>
<tr>
<td>Maternal depression</td>
<td>Further evidence for adverse effects of maternal depressive symptoms on early child development and quality of parenting; community-based interventions with para-professionals effective in reducing depressive symptoms (ES 0.21-0.62)</td>
<td>Increased emphasis on early identification of women who are depressed; programmes to reduce maternal depressive symptoms and reduce risks for depression will probably benefit early child development</td>
</tr>
<tr>
<td>Exposure to violence</td>
<td>Exposure to violence detrimentally affects social–emotional development of young children (ES medium to large) and compromises primary caregiver child-rearing capabilities; some evidence that interventions can reduce stress reactions in young children (ES 0.56-0.93)</td>
<td>Need for interventions that can strengthen families exposed to societal violence and help caregivers reduce effect of exposure on young children</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Substantial evidence that development of infected children is delayed (ES usually medium to large; webappendix pp 33-37); US studies show developmental benefits from HAART, less evidence from low-income and middle-income countries; affected children might also have cognitive deficits and mental health problems</td>
<td>Need for increased coverage with HAART; starting children on treatment in the first year of life, and for assessment of effect of treatment on developmental outcomes</td>
</tr>
<tr>
<td>Institutionalisation</td>
<td>Recent evidence has documented adverse neural, cognitive, and behavioural effects for institutionalised children (ES for IQ 1.10, compared with family reared); improving quality of caregiving in institutions benefits cognitive and social–emotional competence (ES 0.43-0.84)</td>
<td>Strategies are needed to support foster and adoptive families to prevent children being placed in institutions; where children are institutionalised, strategies shown to improve early child development should be implemented</td>
</tr>
</tbody>
</table>

Protective factors

Breastfeeding | Stronger evidence for beneficial effects of exclusively breastfed and longer duration of breastfeeding (ES for IQ 0.38; grades attained 0.22-0.35) | Benefits to development add to existing reasons for promotion of breastfeeding |

Maternal education | Growing evidence on mechanisms linking maternal education to children’s development (ES medium Cohen’s h=0.73 to large Cohen’s h=0.82, d=1.59) | Increased emphasis on educating women as part of an overall intervention package; ensure interventions are appropriate for women with little education |

IUGR=intrauterine growth restriction. ES=effect sizes. HAART=highly active antiretroviral therapy. IQ=intelligence quotient. †ES are for studies reviewed in this paper that reported them or with sufficient information to compute; where specific ES are given, these are Cohen’s d unless otherwise specified (previously reported effect sizes from earlier studies are reported in Walker and colleagues). ‡Not reported as a high priority risk or protective factor in the previous Series in The Lancet.

Table 4: High priority developmental risk and protective factors
Panel 3: Priorities for future research to reduce developmental inequalities in infants and young children from low-income and middle-income countries

Maternal nutrition
- Effect of food supplementation before and during pregnancy on development of infants and young children.
- Effect of prenatal iron deficiency on postnatal cognitive and social–emotional development.
- Effect of supplementation with multiple micronutrients in pregnancy on child development by comparison with iron and folic acid alone.
- Effect of maternal supplementation with ω3 fatty acids on infant development.
- Long-term effects of IUGR on cognitive and social–emotional outcomes.

Child nutrition
- Effect of improving infant intake of essential fatty acids on development.
- Effect of supplementation with multiple micronutrients on development and comparison with effects of iron only.
- How to integrate nutrition and psychosocial stimulation programmes at scale.

Infections
- Effect of malaria prevention strategies on early child development.
- Effect of antiretroviral treatment on cognitive and behavioural outcomes and effect of non-medical interventions to promote development in children infected with HIV.
- Extent of mental health problems for infants and young children orphaned because of AIDS. Assessment of interventions to support caregivers and promote development of children affected by HIV.

Toxins
- Evidence on effect of toxins is inconsistent possibly because of interactions with other exposures. Longitudinal studies are needed to assess potential moderating variables (eg, nutrition).

Disabilities
- Assessment of the effect of interventions for children with disability and their families.
- Identification of barriers to accessing general services (eg, primary health care) as well as specialist services.

Learning opportunities and stimulation
- Modification of interventions to facilitate expansion, and assessment of effectiveness of programmes at scale.
- More evidence on the effect of early interventions on social and emotional development.

Maternal depression
- Assessment of effect of interventions to reduce depressive symptoms on child development and identification of strategies to expand access.

Violence
- Evidence needed on the neural and developmental effect of violence exposure on children younger than 5 years and on effective treatment strategies for young children exposed to violence.

Protective factors
- Need to identify additional protective factors for outcomes related to early child development in low-income and middle-income countries.

the importance of integrated interventions involving the simultaneous reduction of multiple risks. The second paper in the Series discusses integrated interventions.

Inequalities in low-income and middle-income countries are established in early childhood and contribute to lifetime differences. Accumulated developmental deficits in early childhood place children on a lower lifetime trajectory with negative implications for adult cognitive and psychological functioning, educational attainment, and subsequent income, thus contributing to continued inequalities in the next generation.

In table 4, we list the risk and protective factors with sufficient evidence to be priorities for intervention and summarise the evidence reviewed. Previously identified key risks (inadequate stimulation, stunting, iodine deficiency, iron-deficiency anaemia) remain in need of urgent intervention to prevent the loss of developmental potential in millions of young children. Although there has been recent attention to the effect of early nutrition on development and health, substantial progress in improving development is unlikely to be made without also increasing early learning opportunities. A meta-analysis of non-US intervention studies showed that cognitive benefits were greater when interventions included stimulation or education components compared with those comprising nutrition or economic assistance only. This strengthens the case for integration of stimulation with economic, nutrition, and health interventions.

New research strengthens the evidence for prioritisation of interventions to reduce the levels of IUGR, malaria, maternal depression, institutionalisation, and exposure to societal violence and to promote development in affected children. New research also suggests the adverse consequences for children infected with HIV or whose parents are infected. We highlight the importance of protective factors such as breastfeeding and higher maternal education, which can reduce the effect of risks. Knowledge of risk and protective factors can inform priorities for programmes and funding to promote early child development. This knowledge, plus increased understanding of the neural consequences of risks, provides persuasive data for advocacy and the design of early intervention programmes to reduce developmental inequalities.

Although effective interventions exist for some identified risks, further research is needed to increase our ability to promote early child development in low-income and middle-income countries. We list research priorities in panel 3. There has been little progress in some previously identified research priorities (eg, supplementation with multiple micronutrients, prenatal iron deficiency, and exposure to toxins). Additional research questions include the effect of prenatal maternal nutrition and stress on development, assessment of the effect of interventions to reduce maternal depression on child development, and assessment of strategies to reduce the
developmental consequences for children affected by violence and for children in families affected by HIV. Research is also needed to develop strategies to include children with disabilities in early child development programmes and provide them with specialist services, and to identify additional protective factors in low-income and middle-income countries.

Without the threats of biological and psychosocial risks, and with a caregiving environment that supports cognitive and social-emotional development, children experience healthy brain development that enables them to reach toward their developmental potential. With this strong foundation, they build lifespan developmental trajectories that enable them to benefit from family, community, and educational opportunities (figure 2). Effective interventions to promote early child development in low-income and middle-income countries exist either at scale or are potentially scalable. Interventions to reduce risks and support early child development will yield lifetime gains that contribute to the achievement and sustainability of improved development in the next generation. By investing in early child development programmes, we have an opportunity to break the cycle of inequities that has dominated the lives of millions of children and families in low-income and middle-income countries.

Contributors
All authors participated in the review of published work, and drafting and review of the report. SPW and TDW are the lead authors of this report and were responsible for the final draft and the decision to submit for publication. SG-M and MMB provided critical revision of the text. Reviews and drafting of individual topics were as follows: Brain development CAN and TDW; maternal undernutrition SG-M; micronutrients SG-M and MMB; essential fatty acids SLH; IUGR SPW; breastfeeding CAP; stunting SG-M; iron deficiency BL; diarrhoea MMB; malaria SG-M; other parasitic infections TDW; HIV JMM and LR; toxins JDH; disabilities HB-H; early learning opportunities SPW, SMC, and HBH; maternal depression AR; violence JMM and TDW; institutionalisation CAN, SG-M, and LR; and protective factors TDW. The steering committee of the Global Child Development Group coordinated the writing of the report in this Series.

Conflicts of interest
We declare that we have no conflicts of interest.

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