Advancing Early Childhood Development: from Science to Scale 2



Nurturing care: promoting early childhood development

Pia R Britto, Stephen J Lye, Kerrie Proulx, Aisha K Yousafzai, Stephen G Matthews, Tyler Vaivada, Rafael Perez-Escamilla, Nirmala Rao, Patrick Ip, Lia C H Fernald, Harriet MacMillan, Mark Hanson, Theodore D Wachs, Haogen Yao, Hirokazu Yoshikawa, Adrian Cerezo, James F Leckman, Zulfiqar A Bhutta, and the Early Childhood Development Interventions Review Group, for the Lancet Early Childhood Development Series Steering Committee*

The UN Sustainable Development Goals provide a historic opportunity to implement interventions, at scale, to promote early childhood development. Although the evidence base for the importance of early childhood development has grown, the research is distributed across sectors, populations, and settings, with diversity noted in both scope and focus. We provide a comprehensive updated analysis of early childhood development interventions across the five sectors of health, nutrition, education, child protection, and social protection. Our review concludes that to make interventions successful, smart, and sustainable, they need to be implemented as multi-sectoral intervention packages anchored in nurturing care. The recommendations emphasise that intervention packages should be applied at developmentally appropriate times during the life course, target multiple risks, and build on existing delivery platforms for feasibility of scale-up. While interventions will continue to improve with the growth of developmental science, the evidence now strongly suggests that parents, caregivers, and families need to be supported in providing nurturing care and protection in order for young children to achieve their developmental potential.

Introduction

Although global attention to early childhood development has been established through its inclusion in the UN Sustainable Development Goals, 250 million children (43%) younger than 5 years in low-income and middle-income countries are at risk of not achieving their developmental potential, as discussed in Paper 1 of this Series.¹ We suggest that this gap in human potential is partly due to two reasons: the failure to apply emerging scientific knowledge on nurturing care to shape young children's development; and the failure to take action at scale, using a multi-sector approach across key stages in the early life course.

We define nurturing care as a stable environment that is sensitive to children's health and nutritional needs, with protection from threats, opportunities for early learning, and interactions that are responsive, emotionally supportive, and developmentally stimulating. As an overarching concept, nurturing care is supported by a large array of social contexts—from home to parental work, child care, schooling, the wider community, and policy influences.2 Nurturing care consists of a core set of inter-related components, including: behaviours, attitudes, and knowledge regarding caregiving (eg, health, hygiene care, and feeding care); stimulation (eg, talking, singing, and playing); responsiveness (eg, early bonding, secure attachment, trust, and sensitive communication); and safety (eg, routines and protection from harm).3,4 The single most powerful context for nurturing care is the immediate home and care settings of young children often provided by mothers, but also by fathers and other family members, as well as by child-care services.

The brain has evolved to adapt in response to a wide range of early experiences, which supports the rapid acquisition of language, cognitive skills, and socioemotional competencies. Nurturing care mediates the development of key brain regions and promotes developmental adaptations. These developments have lifelong benefits for children, including an increased ability to learn, greater achievement in school and later life, citizenship, involvement in community activities, and overall quality of life. ^{5,6} The period of early development is

Lancet 2017: 389: 91-102

Published Online
October 4, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)31390-3

This is the second in a **Series** of three papers about early childhood development

*Members listed at the end of the report UNICEF, 3 UN Plaza, New York,

NY, USA (PR Britto PhD); Fraser Mustard Institute for Human

Development (Prof S J Lye PhD, K Proulx PhD, K Proulx PhD, Prof S G Matthews PhD) and Departments of Physiology, Obstetrics and Gynecology, and Medicine, University of Toronto, ON, Canada (Prof S J Lye, Prof S G Matthews); Department of Global Health and Population, Harvard T H Chan School of Public Health, Boston, MA, USA (Prof A K Yousafzai PhD);

Key messages

- Advances in basic and intervention science indicate that early childhood is a period of special sensitivity to experiences that promote development, and that critical time windows exist when the benefits of early childhood development interventions are amplified.
- The most fundamental promotive experiences in the early years of life come from nurturing care and protection received from parents, family, and community, which have lifelong benefits including improved health and wellbeing, and increased ability to learn and earn.
- Nurturing care and protection are supported by a range of interventions delivered prepregnancy and throughout birth and the newborn period, infancy, and early childhood.
 Many of these interventions have shown benefits for child development, nutrition, and growth, and reductions in morbidity, mortality, disability, and injury.
- Interventions that integrate nurturing care and protection can target multiple risks to developmental potential at appropriate times, and can be integrated within existing preventive and promotive packages.
- Preventive and promotive packages can build on existing platforms, such as community-based strategies and social safety nets, for delivering parental and child services at scale to vulnerable and difficult-to-reach populations, enhancing their effectiveness and sustainability.

Center of Excellence in Women and Child Health. The Aga Khan University, Karachi, Pakistan (Prof Z A Bhutta PhD); Center for Global Child Health, The Hospital for Sick Children, Toronto, ON, Canada (Prof Z A Bhutta, T Vaivada MSc): Department of Chronic Disease Epidemiology, Yale School of **Public Health** (Prof R Perez-Escamilla PhD), and Yale Child Study Centre. Yale School of Medicine, Yale University, CT, USA (JF Leckman MD); Faculty of Education (Prof N Rao PhD) and Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine. The University of Hong Kong. Hong Kong (P Ip FRCPCH); School of Public Health, University of California Berkeley, Berkeley, CA, USA (Prof L C H Fernald PhD); Department of Psychiatry and Behavioural Neurosciences, and Department of Pediatrics, Offord Centre for Child Studies, McMaster University, Hamilton, ON, Canada (Prof H MacMillan MD); Institute of Developmental Sciences and NIHR Biomedical Research Centre, University of Southampton and University Hospital Southampton, UK (Prof M Hanson DPhil); Department of Psychological Sciences, Purdue University. West Lafayette, IN, USA (Prof T D Wachs PhD); Teachers College, Columbia University, New York NY USA (H Yao PhD) **New York University** Steinhardt, New York, NY, USA (Prof H Yoshikawa PhD): and Department of Biology. University of Missouri, St Louis, MO, USA (A Cerezo PhD)

Correspondence to:
Pia Rebello Britto, Senior
Advisor, UNICEF, 3 UN Plaza,
New York, NY 10017, USA
pbritto@unicef.org

See Online for appendix

one of enormous change and is characterised by a high degree of plasticity in brain organisation.^{7,8} Advances in developmental science have also provided an understanding of the multiple and overlapping critical windows of time when development of specific capacities and abilities is most powerfully enhanced. 9,10 Nurturing, caring, enriching, and protective interactions provide the early environments needed for developmental progression to occur, and protect infants and children from the negative effect of stress and adversity (panel 1). Studies from across the globe, including from Jamaica, 17-19 Pakistan.20 and Turkey.21,22 have demonstrated that including elements of nurturing care in interventions significantly improves childhood development and even later adult outcomes (appendix pp 22-25). The interplay between the elements of nurturing care, the timing of experiences, and complexity of risks requires action beyond single sector interventions.

Selection of interventions for review

This paper provides a comprehensive update of early childhood development interventions across key sectors. Although progress has been made with early childhood development-related interventions, existing research is at different levels of maturity across sectors and distributed across numerous populations and settings. Experts from research communities in reproductive, maternal, newborn, and child health (RMNCH), nutrition, parenting, early childhood education, maltreatment prevention, and social protection worked in teams using standard methods to critically appraise the available evidence that addressed child outcomes, including: mortality; malformations, disability, and injury; nutrition and growth; and severe morbidity (panel 2). The primary focus, however, was direct measures of child development outcomes (eg, language, cognition, motor, social and emotional development, and psychosocial wellbeing). Most papers in each sector were published after the last Lancet Series on early childhood development-ie, from October, 2011, to April, 2015. Search strategies in each group were tailored to the existing evidence in each sector. The RMNCH and nutrition group relied on the most recent overviews of systematic reviews featuring good quality methods for all interventions, and updated the evidence by incorporating newer studies, when available. The parenting and early childhood education, child protection, and social protection groups relied on the most recent systematic reviews, and incorporated newer studies, when available. From preconception to birth, the focus of the interventions is primarily on the maternal caregiver. From birth throughout infancy, interventions typically include both adult and child, and in the age period transitioning into primary school (between the ages 6 and 8, depending on the country), we note a predominantly child-focused set of interventions with increasing emphasis on the importance of a nurturing environment provided by teachers. Details of the search methods used for selecting and screening reviews are described in panel 2.

Interventions encompassing the period before conception to birth

We did a comprehensive review of 40 interventions related to early childhood development across diverse sectors, and found 15 types of interventions that show benefit on multiple outcomes including child development, based on high-quality systematic reviews (table). Many of those with effects on childhood development encompass aspects of nurturing care including parenting support and social protection, care for the caregiver, and early learning opportunities provided in or out of the home environment.

Maternal health

While nurturing care interventions usually begin at birth, established RMNCH interventions can reduce adverse growth and health outcomes-including stunting, low birthweight, and iron deficiency anaemiathat are strongly related to early childhood development. In our review of low-income and middle-income countries (LMICs), we identified five such RMNCH interventions during the period from preconception to birth and labour that have significant effects on child development, in addition to growth, mortality, morbidity, or disability (appendix pp 2-9). These interventions include: iodine supplementation before or during pregnancy,56 antenatal corticosteroids for women at risk of preterm birth,57 magnesium sulphate for women at risk of preterm birth,58 antiplatelet drugs for women at risk of pre-eclampsia, 59 and therapeutic hypothermia 60 for hypoxic ischaemic encephalopathy. One review⁶¹ found mixed effects of delayed cord clamping on measures of neurodevelopment at 4 months, based on the results of one study. 62 Tobacco and alcohol use are viewed as serious threats to the health of pregnant women and their children. A review of 86 randomised controlled trials showed that psychosocial programmes have been successful during pregnancy for smoking cessation, reducing low birthweight and preterm births, but evidence is limited on such interventions in LMICs.63

Maternal nutrition, micronutrients, and iodine supplementation

The ability of a mother to support the health and development of her children is critically dependent on her own health and wellbeing before, during, and after pregnancy. Intrauterine growth restriction influences multiple aspects of child development and has been linked to poorer neurodevelopmental outcomes, risks of prematurity, reduced school performance, and heightened behavioural problems in children. Evidence suggests that linear growth is correlated across generations and short maternal stature is associated with low birthweight, stunting, childbirth complications, and increased child mortality. The provision of a balanced energy and protein

Panel 1: Co-occurrences among bio-ecological or contextual risk factors in low-income and middle-income countries

Although there are parallels in the types of risk and promotive factors encountered by children in high-income, middle-income, and low-income countries, the limited evidence indicates that children from low-income and middle-income countries (LMICs) are more likely to encounter a greater number and range of risk factors and fewer promotive influences for development than poor children in high-income countries (HICs). 11,12 Toxins, chronic severe malnutrition, direct exposures to armed conflict and displacement, and refugee status are risk factors that occur in LMICs, but are rarely seen in HICs. Exposure to environmental factors that reduce blood-brain barrier integrity will decrease protection of the developing brain. Poor sanitation, severe childhood diarrhoea, iron deficiency anaemia, orphan status, substandard housing, domestic violence, harsh physical punishment, and maternal depression are risk factors that occur at a higher rate in LMICs than in HICs and can be frequently amplified by exposure to conflict and population displacement. Some evidence indicates that there might be a reduced availability of promotive factors in LMICs, such as routine neonatal screening for iodine deficiency, 13 childbirth attended by skilled health personnel, 14 and fewer learning resources in the home. 15 In addition to a greater range and prevalence, there are higher levels of co-occurrence among risk factors in LMICs compared with HICs.16 Based on analysis of UNICEF Multiple Indicator Cluster Survey data, multiple risk factors co-occur. For example, 85% of children aged 3-4 years in west and central Africa and 56% in east Asia and Pacific experience multiple risks. Data estimating risks for children living in conflict, crises, and insecure conditions are scant; however, we estimate increased levels of co-occurrence of risk factors in such situations. The findings support the application of coordination or combining of interventions, within packages, to reduce exposure to multiple risk factors. The following are specific examples of co-occurrence.

Nutritional deficiencies in infancy and early childhood are likely to occur with:

- Being born small for gestational age, or preterm, or both
- Parents who are less involved, sensitive, or responsive to the needs of the child
- Extreme poverty and food insecurity
- Suboptimal infant and young child feeding practices
- High exposure to pathogens and corresponding burden of infectious disease in infancy and childhood
- Home environments characterised as less stimulating than others
- Exposure to domestic violence

Maternal depression and anxiety are likely to coexist with:

- · Preterm birth
- Low birthweight
- Poor infant growth and reduced cognitive development
- Less adequate prenatal care
- Less adequate caregiving including:
- Suboptimal infant and child feeding practices (including not exclusive breastfeeding)
- Insufficient communication and play to stimulate learning
- Delayed and inappropriate care-seeking
- · Increased child morbidity
- Increased use of harsh discipline
- Increased family stress

Exposure to societal violence is likely to occur with:

- · Child abuse and neglectful parenting
- Disruption of family or community support systems
- Disrupted and dysfunctional health systems

diet, 66 as well as multiple micronutrients, 67 for women of childbearing age and expectant mothers at risk of deficiencies shows potential benefits in reducing the risk of intrauterine growth restriction, small-for-gestational-age births, and stillbirths (appendix pp 2–9). Iron and iron-folate supplementation during pregnancy reduces the risk of small-for-gestational-age and premature births, 68 while folic acid fortification is associated with prevention of neural tube defects and risk of adverse birth outcomes. 69 Iodine supplementation in moderate-to-severely iodine deficient areas is the only nutrition-related intervention during pregnancy with evidence of a significant effect on children's cognitive development scores, increasing them by 10–20%. 56

Maternal stress, depression, and mental disorders

The onset of caregiving in humans is triggered by hormonal signals beginning in pregnancy (eg, oxytocin and lactogens).⁷⁰ Mental disorders and the timing of stress during pregnancy can disrupt maternal programming, which prepares women to respond to their infants, and

can have negative effects on the fetus.71 Disruption to maternal programming might account for associations between maternal mental disorders, insecure motherinfant attachment, and exposure to maltreatment. Mental disorders in women, including depression and anxiety, are among the most common conditions to coexist with pregnancy and are associated with a range of negative child outcomes, including poor infant growth, children's emotional and behavioural difficulties, and insecure attachment with caregivers.71 Recent evidence is emerging that paternal mental health during pregnancy can also influence the socioemotional and behavioural development of children.⁷² A systematic review of 13 trials of psychological interventions, delivered by local community health workers, for women with antenatal depression in LMICs showed positive effects on reducing maternal depression.73 Benefits to children included improved mother-infant interaction, improved cognitive development and growth, reduced frequency of diarrhoea episodes, and increased immunisation rates. Antidepressants for treatment of antenatal depression have

Panel 2: Criteria for identifying relevant research

We identified peer-reviewed overviews, systematic reviews, and individual studies that focused primarily on child development outcomes, published between January, 2009, and April, 2015. We used established guidelines to search, evaluate, and synthesise the results of relevant research.²³ The reproductive maternal, newborn, and child health and nutrition reviews relied primarily on six recent overviews of reviews, including: the Lancet Breastfeeding Series (2016);²⁴ the Lancet Every Newborn Series (2014);²⁵ the Lancet Maternal and Child Nutrition Series (2013);²⁶ the Lancet Childhood Pneumonia and Diarrhoea Series (2013);²⁷ the Reproductive Health 2014 supplement on essential maternal, newborn, and child health interventions;28 and the Essential Interventions for Reproductive, Maternal, Newborn, and Child Health report by the Partnership for Maternal, Newborn and Child Health (2011).²⁹ The education review was based on four recent reviews, including: the Lancet Child Development in Developing Countries Series (2011);30 a systematic review of parenting interventions published by the Annual Review of Psychology (2015);31 a literature review of parenting and early childhood programmes (2014);32 and a Cochrane review of centre-based day care for children under 5 (2014).33 A meta-analysis of education programmes was conducted to determine non-cognitive developmental benefits of parenting and early childhood education programmes, as this information was not available in existing systematic reviews. The review of maltreatment prevention publications updated the Lancet article on prevention of child maltreatment (2009)³⁴ and a systematic review of child maltreatment prevention reviews.³⁵ by including recent reviews of maltreatment prevention interventions, 32,34-45 such as home visiting, 37-39 parenting training programmes, 40,41 sexual abuse prevention programmes, 42,43 universal campaigns to prevent physical abuse, 44 behavioural and counselling interventions, 45 detection of child maltreatment, 46 and three narrative reviews on prevention of child maltreatment.⁴⁷⁻⁴⁹ The social protection literature review examined five systematic reviews that focused on the effects of social programmes, including conditional and unconditional cash transfers and microcredit schemes. 50,51,53,54 After examining the systematic reviews, the literature was searched for papers that had been published since the systematic reviews. 24 new studies were included that investigated the effects of conditional cash transfers or unconditional cash transfers on measures of health, nutrition, or developmental outcomes. The search focused on research conducted in low-income and middle-income countries (LMICs), but systematic reviews based on evidence from high-income countries were included for maltreatment prevention where evidence from LMICs was either unavailable or limited. Data were double-extracted using a standardised form. Methodological quality of systematic reviews was assessed using the AMSTAR criteria, where appropriate.55 More detailed information on the search strategies for each review topic can be found in the supplementary appendix.

For more on the Care for Child p

Development Package see http:// C

www.unicef.org/earlychildhood/
index 68195.html

For more on **Reach Up and Learn** see http://www.reachupandlearn.com been associated with small but significant increases in preterm birth and reductions in birthweight.^{74,75} Persistence of depression into the postnatal period and beyond seems to be of particular importance in relation to poorer cognitive development in children, including achievement of developmental milestones, and language development.⁷¹ Recent trials from Uganda⁷⁶ and Bangladesh⁷⁷ suggest that group-based parenting programmes can improve maternal mental health in community settings as well as young children's cognitive and receptive language scores. However, more analysis is needed to determine which characteristics of maternal health interventions are associated with improved maternal wellbeing and issues of scalability.

Living in poverty is associated with a high degree of stress. Conditional cash transfer programmes have increased the proportion of people receiving prenatal care, probability of in-facility birth and of having a skilled birth attendant, 52 conditions often associated with improved birth outcomes (ie, decreased neonatal mortality) and later developmental outcomes. During labour and childbirth, mothers who have continuous social support (eg, emotional support, comfort measures, information, and advocacy) show significantly more positive clinical benefits for themselves and for their infants compared with mothers who don't.78

Interventions from birth to 5 years of age Parenting support

Opportunities for stimulation, responsive parent-child interactions, child-directed and focused enrichment, early learning, and positive parenting are crucial for children's development.³⁰ Parenting programmes are operationally defined as interventions or services aimed at improving parenting interactions, behaviours, knowledge, beliefs, attitudes, and practices. Three recent reviews31,32,36 of parenting programmes in LMICs found positive effects on direct measures of children's cognitive and language development across diverse policy, service delivery, and social contexts. We updated and expanded on the previous reviews by conducting a meta-analysis of non-cognitive outcomes and concluded that parenting programmes increased scores on measures of psychosocial development (standardised mean difference [SMD] 0.35, 95% CI 0·14-0·56, 13 studies) and motor development (0.13, 0.07-0.19, nine studies), in addition to child cognitive development (0.36, 0.22-0.49, 19 studies) (appendix pp 10–15). The effect of parenting programmes on child growth was not significant.

Parenting programme implementation varied in relation to dose of intervention, setting, and curriculum. The total amount of contact with parents, which ranged from less than 10 h to 120 h, did not have a clear association with the size of effect.³² Some programme models have used only home visits-eg, Roving Caregivers in Jamaica79—and others, such as Pastoral del Niño in Paraguay, have used group sessions.80 Combined group sessions and home visits in Bangladesh⁸¹ and Brazil⁸² produced better outcomes than did home visits alone. The most effective parenting programmes used several behaviour-change techniques, including media such as posters and cards that illustrate enrichment practices, opportunities for parental practice of play and responsive talk with their child, guidance and support for changing practices, and problem-solving strategies.31 Examples include the Care for Child Development package developed by UNICEF and WHO, and Reach Up and Learn, which provide opportunities to use multiple strategies to strengthen nurturing care by parents.17 A notable gap in published reviews is the role of fathers in promoting nurturing care and protection.83 Parenting programmes that combine nutrition and stimulation have been effective in improving child cognitive and language development outcomes.31 Taken together, the results suggest that parenting support programmes that promote nurturing care and protection can substantially augment the positive effects of basic health and nutrition, education, and protection interventions on early child development outcomes.

Attachment and bonding

Different brain systems enhance nurturing by supporting infant-mother attachment, as well as emotional wellbeing, learning and memory, attention, and executive functions.84 Secure attachment forms with a caregiver who provides security, safety, affection, and comfort. Aspects of nurturing care during birth and labour include early initiation of breastfeeding and interventions such as Kangaroo Mother Care, which promotes thermal sufficiency in preterm infants, and early bonding. Kangaroo Mother Care has been associated with an increase in bonding indicators such as infant-mother attachment at 3 months (mean difference [MD]=6.24, 95% CI 5.57-6.91), infant growth, and rates of early exclusive breastfeeding (at 1-3 months) (risk ratio [RR]=1.20, 95% CI 1.01-1.43).85 Most of these evaluations were undertaken in health facilities; there is a need for research focusing on effectiveness of Kangaroo Mother Care or variants thereof when delivered at scale in community settings.

Breastfeeding

Breastfeeding has clear short-term benefits for child health, reducing mortality and morbidity from infectious diseases, encouraging healthy food preferences, and promoting the establishment of a healthy gut microbiome.86 A recent review of 17 observational studies of breastfeeding presents evidence that optimal breastfeeding supports improved performance in intelligence tests in childhood and adolescence, demonstrating an intelligence quotient (IQ) increase of 3.44 points (95% CI 2.30–4.58).87 Findings from a 2015 analysis88 of the Pelotas birth cohort in Brazil also showed a dose-response association between breastfeeding duration and increased child intelligence, educational attainment, and income at the age of 30 years. The positive effect of breastfeeding was observed in one randomised trial⁸⁹ in Belarus, in which duration of total and exclusive breastfeeding was higher in the intervention group that received the Baby-Friendly Hospital Initiative than in a control group that was not exposed to the breastfeeding counselling intervention; performance in intelligence tests at 6.5 years was also higher in the intervention group. A cohort analysis from South Africa found that exclusive breastfeeding was associated with fewer than average conduct disorders.90

Micronutrients and child feeding

Malnutrition remains a serious challenge in developing countries, undermining the survival, growth, and development of young children. Stunting and severe acute malnutrition (wasting) are often associated with concomitant micronutrient deficiencies—among these,

	Childhood development	Nutrition and growth	Mortality	Disability, injury, and malformations	Severe morbidity
lodine supplementation before or during pregnancy	✓	✓	✓	✓	
Antenatal corticosteroids for women at risk of preterm birth	✓		✓		✓
Magnesium sulphate for women at risk of preterm birth	✓			✓	
Antiplatelet agents for women at risk of pre-eclampsia	✓	✓	✓		
Therapeutic hypothermia for hypoxic ischaemic encephalopathy	✓		✓	✓	✓
Psychological interventions for common perinatal mental disorders	✓	✓			✓
Iron supplementation in children	✓	✓			
Multiple micronutrient supplementation in children	✓	✓			
Supplementary feeding for disadvantaged children	✓	✓			
Parenting programmes	✓				
Integrated parenting and nutrition programmes	✓	✓			
Out-of-home interventions (pre-primary education)	✓				
Conditional cash transfer	✓	✓	✓		✓
Delayed cord clamping (ie, more placental transfusion)	✓	✓	✓		✓
Breastfeeding promotion, education, or support	✓	✓			
Unconditional cash transfers		✓			✓
Periconceptional folic acid fortification or supplementation				✓	
Birth interval at least 36-60 months		✓	✓		
Preconceptional diabetes care			✓	✓	
Iron and iron-folate supplementation during pregnancy		✓			
Multiple micronutrient supplementation during pregnancy		✓	✓		
Balanced protein-energy supplementation during pregnancy		✓	✓		
Intermittent preventive therapy and use of bednets for malaria prevention in mothers and children		✓	✓		✓
Antibiotics for premature rupture of membranes		✓		✓	✓
Lower genital tract infection screening and treatment in pregnant mothers		✓			
Antibiotics for asymptomatic bacteriuria in children		✓			
				(Table continues o	on next page)

	Childhood development	Nutrition and growth	Mortality	Disability, injury, and malformations	Severe morbidity
(Continued from previous page)					
Detection and treatment of syphilis in pregnant mothers		✓	✓		✓
Smoking cessation interventions in parents		✓			
Continuous support during childbirth	"				✓
Kangaroo Mother Care, skin-to-skin, cap and wrap (thermal care)		✓	✓		✓
Topical emollient therapy for preterm neonates		✓	✓		✓
Intramuscular vitamin K for neonates					✓
Handwashing behaviour and water quality improvement eg, water, sanitation, and hygiene (WASH)	-	✓	✓		✓
Rotavirus, HiB, and pneumococcal vaccinations in children			✓		✓
Vitamin A supplementation in children		✓	✓	✓	✓
Zinc supplementation and treatment for acute diarrhoea in children		✓	✓		✓
Deworming drug treatment in children		✓			
Complementary feeding education and provision		✓			✓
Treatment of moderate and severe acute malnutrition in children		✓			✓
Interventions to prevent child maltreatment (eg, specific home-visiting and parenting programmes)*					

Interventions were for improving child development, nutrition and growth, mortality, disability, and morbidity in low-income and middle-income countries (LMICs), based on high-quality systematic review evidence discussed in text. Checkmarks pertain to significant pooled effect sizes. HiB=Haemophilus influenza type B. *Most rigorous trials of interventions to prevent child maltreatment have been conducted in high-income countries, with far fewer in LMICs, and are not uniformly effective in reducing injuries, physical abuse, and neglect.

Table: Summary of effective interventions related to early childhood development

vitamin A, iron, zinc, and iodine deficiencies are the most prevalent in childhood. Given the wide prevalence of multiple micronutrient deficiencies in malnourished children, there is a need to implement interventions that combine micronutrient interventions with appropriate infant and young child feeding.

One review, limited to four trials, found that multiple micronutrient supplementation in children at risk of deficiencies has also been shown to improve academic performance among children 5–16 years of age (SMD 0.30, 95% CI 0.01 to 0.58). A review of iron supplementation in children found improvement in psychomotor development at 12 months (MD 6.90, 95% CI 1.35 to 12.45) and a decrease in IQ in school grades 1–6 (children of

average age 10 years; MD $-3\cdot00$, $-5\cdot96$ to $-0\cdot04$); ⁹² a second review on iron supplementation found an improvement in mental development (SMD $0\cdot30$, $0\cdot15$ to $0\cdot46$) and IQ (SMD $0\cdot41$, $0\cdot20$ to $0\cdot62$). ⁹³ One other review, which focused on the effect of supplementary food given to socioeconomically disadvantaged children aged from 3 months to 5 years, found that food supplements improved psychomotor development (SMD $0\cdot41$, $0\cdot10$ to $0\cdot72$), but found mixed effects on measures of cognitive development in different trials (SMD $-0\cdot40$, $-0\cdot79$ to 0 for Bayley II: Mental Development; and SMD $0\cdot58$, $0\cdot17$ to $0\cdot98$ for cognitive development test battery). ⁹⁴ Results from individual studies in Bangladesh ⁹⁵ and India ⁹⁶ suggest that responsive feeding can be effective in promoting child growth and developmental outcomes.

Prevention of child maltreatment

Family violence is increasingly recognised as a key public health problem in LMICs. Maltreatment during childhood is associated with reduced volume of both the midsaggital area and hippocampus, which are brain regions involved in learning and memory.97 Children who receive inadequate care, especially in the first 24 months of life, are more sensitive to the effects of stress and display more behavioural problems than do children who receive nurturing care.98 There is increasing evidence that one of the most powerful predictors of caregiving behaviour is how caregivers, especially mothers, were cared for themselves.99 Children who grow up neglected or abused by their parents, or under conditions of extreme distress within their families, are at risk of developing a host of unhealthy behaviours that affect their own lives. When these children grow up, they tend to be less equipped to take on a parenting role and are more likely to perpetuate a cycle of adverse caregiving across generations. The maltreatment prevention interventions with the best evidence that shows positive results following the intervention are selective programmes (eg, Nurse Family Partnership) characterised by intensive visits by professional home visitors and beginning prenatally, but these programmes have not been evaluated in LMICs (appendix pp 16-18). The extent to which these findings are generalised beyond the specific HICs where they have been evaluated is unknown. A systematic review of 12 parenting interventions for reducing harsh or abusive parenting in LMICs found potentially positive results on a range of parenting measures, but the quality of included trials was generally low.40 Early intervention that occurs before the onset of abusive and neglectful parenting is crucial to preventing maltreatment. One specific parenting programme, Triple P, has shown some promise in one HIC randomised trial.100 There is an urgent need for more rigorously evaluated maltreatment prevention interventions in LMICs, focusing on parenting and child outcomes, and adapted for low resource contexts. More recent reviews of early childhood development interventions in LMICs are suggesting associations with violence reduction and peace promotion (appendix pp 26–28).

Out-of-home interventions

Effects of early learning programmes, including highquality child care, and formal and informal preschools, are well established in LMICs.30 On the basis of an update of an earlier published review,32 we found that formal and non-formal or community-based preschools in LMICs improved scores on direct measures of children's cognitive development (SMD=0.67, 95% CI 0.43-0.91, 26 studies) and psychosocial development (0.23, 0.06-0.4, five studies; appendix pp 10-15). The effects of early learning programmes on child growth were not significant and one study measuring motor development showed non-significant effects. The earlier review³² found that the effects of non-formal preschools on child outcomes were typically weaker than those of formal preschools; yet some low-cost and innovative programmes, such as home-based preschool¹⁰¹ and a child-to-child approach,102 improve developmental outcomes in participants compared with nonparticipants. Regardless of type, programme quality is a key predictor of effectiveness; important factors of preschool quality include greater number, variety and challenging play materials, interactive or dialogic reading, classroom organisation, and instructional support. Nurturing environments, in the form of care and positive interactions and individualised attention, appear to be important in early learning programmes. A positive emotional climate at child-care centres in Chile103 and Ecuador,104 including individualised attention, positive affect or positive moods, and reinforcement of children's behaviours, has shown positive associations with children's early childhood cognitive and socioemotional skills.

Social safety net interventions

Our analysis of the systematic reviews⁵⁰⁻⁵⁴ and the new literature (appendix pp 19-21) on social safety net interventions suggests positive effects of conditional cash transfer programmes on some child outcomes, including birthweight, illness, or morbidity. Outcomes with mixed-group or subgroup effects included heightfor-age or stunting, weight-for-age or underweight, and cognitive and language development. Conditional cash transfer programme participation consistently had no effects on haemoglobin concentration or prevalence of anaemia in children. In terms of indirect effects of these programmes, results were significant for effects of participation on prenatal care, growth monitoring, micronutrient supplementation, and household food consumption. It is difficult, however, to compare results across countries and contexts because programmes differ greatly. The effect of cash transfers on child development might be improved by combining social protection early childhood development and interventions. Cash transfer programmes try to address many issues at multiple levels that influence child development, such as parental and community levels, but these programmes do not directly change the factors that are linked with improving development outcomes. For example, programmes providing parental support for child development within the context of larger social protection efforts in Latin America have shown substantial benefits for child development, over and above the benefits of conditional cash transfer programmes. 105,106 Bringing these two interventions together can address both economic and nurturing care factors that impact developmental outcomes.

Intervention packages that integrate nurturing care with sector-specific programmes

Building on the earlier Lancet child development Series, the subsequent literature on early childhood interventions has expanded to include new longitudinal data and cohort data from LMICs. Most interventions during the period from preconception to birth focus on the physical and mental health of the mother to support a healthy pregnancy and improve birth outcomes. Interventions focusing on nurturing care and protection are usually introduced at birth; however, maternal programming for nurturing care begins during pregnancy and even earlier, with the caregiver's own childhood experiences. Evidence-based interventions during infancy that combine basic sectoral elements in health, nutrition, child and social protection, and child care and learning, with nurturing care and protection can synergistically improve child developmental outcomes. For example, including stimulation in nutrition programmes can improve developmental outcomes, which cannot be fully promoted through nutrition interventions alone.31 Breastfeeding is an example of an intervention that combines elements of nutrition with bonding.

Building on sectoral services

Multi-sector approaches include coordinated services across sectors, for example water and sanitation, ideally with unifying policies. Integrated approaches refer to integration across services with shared messages and opportunities for synergy, as discussed in Paper 1 of this Series. Many sectoral interventions could serve as the basis for delivery of services that link policy level strategies of cash transfer, social policies, and income generation with programmatic interventions, such as parenting support, that could benefit childhood development (appendix pp 19-21). Sectors were not included in this review, as further research is needed to examine their effects on developmental outcomes. However, associations have been noted between these sectoral interventions and such outcomes as child nutritional status, growth, and health.80-82

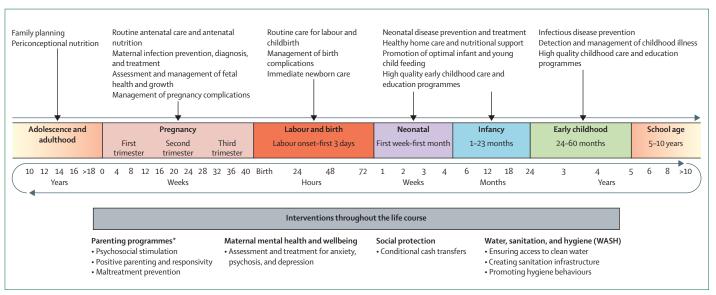


Figure: Evidence-based interventions that affect aspects of nurturing care

Delivering multi-sectoral intervention packages to improve childhood development

The effect of interventions on early childhood development could be improved by taking into consideration the major insights we have gained over the past decade about how human development is affected by complex and multi-faceted experiences, starting with previous generations. Based on the science of early human development, we need to conceptualise meaningful integration of interventions through a coordinated approach. In instances in which sectoral interventions were combined with elements of nurturing care and protection-eg, the Care for Child Development Programme delivered by Lady Health Workers in Pakistan—the effect of the intervention on child outcomes increased significantly.20 This approach allows us to intervene with the family as a unit rather than the child alone. Furthermore, there are increasing opportunities to improve interventions by combining them with nurturing care and protection, through parenting support and skills programmes.

Previous attempts at creating packages of effective interventions have focused either on the temporal relevance of the interventions (ie, packaging interventions that co-occur during the same age period of the child)¹⁰⁷ or on the delivery of the programmes through the same system (eg, maternal, newborn, and child health). Although it is important to consider these factors, we also need to incorporate nurturing care and protection into the packages and tailor them to unique sets of risks and adversities facing the young child population particular to the setting.

Based on our review, we propose three illustrative packages that build on these principles and the findings. These interventions affect different aspects of nurturing care and cover numerous domains and stages in the life course (figure).

Family support and strengthening package

There are three elements of family strengthening: (access to quality services (eg, antenatal care, immunisation, and nutrition); skills building (eg, positive and responsive parenting to reduce harsh discipline and promote stimulation); and support (eg, social protection, safety networks, and family support policies). These elements increase the likelihood that families are better able to provide nurturing care for their children. Each of these skills, elements—services, and support—have independent predictive effects, however significant positive effects are seen when they are combined with programmatic interventions (eg, social protection interventions). By creating a package of the three elements of services, support, and skill building, based on the age of the child and nature of bio-ecological and contextual risk factors, developmental outcomes could be substantially improved.

Multi-generational nurturing care package

This two generation package emphasises care and protection of the mother's and father's physical and mental health and wellbeing, while enhancing their capacity to provide nurturing care to their child. This package combines the essential interventions of health and nutrition for mother and child—primarily delivered by the health-care system from pre-conception up until the first 1000 days of a child's life—and the elements of care, responsivity, stimulation, and protection. This package can be further strengthened with parental leave policies as discussed in Paper 3 of this Series. While the reviews did not specifically cover situations of conflict

and violence, this package is also relevant for humanitarian contexts (panel 3). Conflict, violence, and insecurity present a complex array of adversities. In these settings families, parents, and caregivers require a package of services that addresses their needs as well as the immediate and long-term needs of their children.

Early learning and protection package

This set of interventions integrates the support for young children with parental support and the facilitation of teachers' and caregivers' ability to create a nurturing environment in early childhood centres, classrooms, and community settings for learning. This package of interventions should include nurturing care and protection by enhancing teachers' capacities to proving a nurturing, safe, and positive emotional climate, and should include greater attention to parental support. Long-term gains have been noted when early learning packages have included parenting support and protection for young children.²¹ This package needs to emphasise quality and family support through parental empowerment, guidance on nutrition and care, and child protection.

There are advantages of such integrated packages in terms of delivery; for example, one location can be used for the provision of key services for young children. Identification of platforms at community, clinic, and school levels can be used to coordinate the delivery of the packages targeting population segments and families in greatest need. For example, community platforms that mobilise antenatal and postnatal home visits by community health workers complement facility-based care and promote family contact with the health-care system at crucial times. Social protection platforms provide the opportunity for identification of families in need and delivery of packages of services that link these policies with programmatic interventions. Factors that affect the selection of intervention include the age group being targeted, the expertise of the sector, coverage, or an analysis of the most efficient and effective use of resources within a service for a particular context. More evaluation is needed to codify the interventions to consolidate them into essential packages and assess effectiveness, implementation quality, and cost-benefits of integrated, inter-sectoral, and multi-sectoral approaches for early childhood development packages. Delivery of multisectoral services involves challenges, including limited workforce capacity, demonstration of value added for including programmatic interventions of nurturing care, and political will. Some of these challenges are discussed in Paper 3 of this Series. 108

Future research areas

Although there has been progress in the understanding of what interventions work, there are major gaps in knowledge. The particular set of risks faced by children in conflict is not well understood. There is also a lack of knowledge about the effectiveness of early childhood

Panel 3: Early childhood development interventions for violence prevention and peace promotion

Early parent-child programmes aimed at enhancing responsive parenting can reduce adverse childhood experiences—eg, poor nutrition, neglect, abuse, and exposure to violence in the home—and can positively affect the child's cognitive and socioemotional development, their brain structure and function, and their physical health. Although the published medical literature on implementing early childhood development interventions in contexts of conflict and fragility is limited, the theoretical and empirical underpinnings are strong.

The biobehavioural systems that underlie the development of parent-child relationships are ancient and deeply rooted in mammalian evolution, and are also highly adaptable to changes in the environment. For example, exposure to violence in the home environment and other adverse childhood experiences are associated with changes in brain structure and function in children. ^{109,110} Unfortunately, these children are also at an increased risk of becoming perpetrators of violence as they grow older, so that violence can become self-perpetuating from generation to generation. The biological underpinnings of these phenomena are likely to involve epigenetic mechanisms. Despite an ever-growing body of research, there is still a long way to go before the role of the epigenome in shaping human behaviour across generations is fully understood. If consistent findings emerge, they will provide a solid foundation for the hypothesis that interventions to strengthen families, promote nurturing care and protection, and to improve the cognitive and socioemotional wellbeing of children have trans-generational consequences (appendix).

development interventions in conflict-affected and fragile countries. We need to improve our understanding of how to: better combine interventions through robust assessment of intervention outcomes and evaluations of integrated parenting, responsive care, stimulation, mental health, education and protection interventions that could be delivered through community platforms; use technology-based platforms to deliver effective interventions (appendix pp 29–31); and how to scale up using evidence-based approaches.

Conclusion

In this paper we call for meaningful integration across sectoral interventions, through programmatic packages that promote nurturing care and protection to improve developmental outcomes. We also call for better integration of evidence-based interventions within health-care and nutrition sectors. The results of our literature review suggest that successful, smart, and sustainable interventions to improve developmental outcomes need to: promote nurturing care and protection; be implemented as packages that target multiple risks; be applied at developmentally appropriate times during the life course; be of high quality; and build on existing delivery platforms to enhance feasibility of scaling up and sustainability. We have proposed illustrative packages that meet these requirements. The nature of these interventions will continue to progress as new understanding of early human development emerges. Although questions remain about scaling up interventions at a population level, as discussed by Richter and colleagues in Paper 3 of this Series, 108 we are now at a historic juncture; the evidence is clear about what

needs to be done to improve the wellbeing of future generations, and the political commitment to this is strong, as expressed by the adoption of the Sustainable Development Goals. The science is clear and the evidence convincing that our earliest experiences matter; the Sustainable Development Goals provide a crucial opportunity for implementation. We must draw on this knowledge to take action to support parents, caregivers, and families in providing the nurturing care and protection that young children deserve.

Contributors

PRB and SJL conceptualised the review in consultation with the Early Childhood Development Series Steering Committee and wrote the first draft of the Series paper with substantial inputs from KP. ZAB, RP-E, MFG, and TV led the review of MCNH and nutrition interventions. NR, PI, and AKY led the review of early childhood education and parenting interventions. HM led the review of child maltreatment prevention interventions. LCHF led the review of social protection interventions. SGM, AC, AF, and VGM contributed to the scientific literature review of nurturing care and human development. TDW and HYa reviewed the literature on cumulative and protective risk factors. All authors and members of the review groups saw successive drafts of the paper and provided input. PRB, SJL, and KP prepared the final version of the Series paper, which all authors approved. PRB had final responsibility for the decision to submit for publication.

Early Childhood Development Interventions Review Group

Michelle F Gaffey (Hospital for Sick Children, Toronto, Canada), Kristin Connor, Andrea Constantinof, Alison Fleming, Kristy Hackett, Alison Mildo, Vasilis G Moisiadis, Daniel W Sellen (University of Toronto, Toronto, ON, Canada), Chris McKee (Offord Centre for Child Studies, McMaster University, Hamilton, Canada), Jen MacGregor (Western University, London, Canada).

Early Child Development Series Steering Committee

Zulfiqar A Bhutta, Maureen M Black, Pia R Britto, Bernadette Daelmans, Gary L Darmstadt, Tarun Dua, Paul Gertler, Jody Heymann, Joan Lombardi, Florencia Lopez Boo, Stephen J Lye, Harriet MacMillan, Rafael Perez-Escamilla, Nirmala Rao, Linda M Richter. The Steering Committee provided advice in a meeting with Series Coordinators for each paper at the beginning of the process to prepare the Series, and in regular meetings to review and critique the draft reports.

Declaration of interests

PRB is employed by UNICEF. JFL has received several contracts, gifts, and grants focused on the impact of early child development programmes from UNICEF, the Anne Çocuk Eğitim Vakfı (AÇEV, Mother-Child Education Foundation), the UBS Optimus Foundation, and the Open Road Alliance. The other authors declare that they have no conflicts of interest. The views expressed are those of the authors and not necessarily those of UNICEF, Bill & Melinda Gates Foundation, and Conrad N Hilton Foundation. As corresponding author, PRB states that she had full access to all data and final responsibility to submit for publication.

Acknowledgments

Funding for the preparation of the Series, including three meetings of the authors, was provided by the Bill & Melinda Gates Foundation and the Conrad N Hilton Foundation through the US Fund for UNICEF and WHO, respectively. The sponsors had no role in conceptualising, analysing, interpreting, or writing the paper. We thank the Faculty of Medicine, University of Toronto, for supporting the meeting in Toronto, ON, Canada. The sponsors had no role in the analysis and interpretation of the evidence or in writing the paper and the decision to submit for publication. We thank UNICEF for support to PRB during the course of this work and the British Heart Foundation for support to MH.

References

Black MM, Walker SP, Fernald LC, et al, for the Lancet Early Childhood Development Series Steering Commitee. Early childhood development coming of age: science through the life course. Lancet 2016; published online Oct 4. http://dx.doi. org/10.1016/S0140-6736(16)31389-7.

- Shonkoff JP, Phillips DA, eds. From neurons to neighborhoods: the science of early childhood development. Washington, DC: National Academies Press (US), 2000.
- Bornstein MH, ed. Handbook of Parenting. New York, NY: Psychology Press, 2012.
- 4 Britto PR, Engle P. Parenting education and support: maximizing the most critical enabling environment. In: Marope PTM, Kaga Y, eds. Investing against evidence: the global state of early childhood care and education. Paris: United Nations Educational, Scientific and Cultural Organization, 2015: 157–76.
- 5 Boivin M, Bierman KL, eds. Promoting school readiness and early learning: implications of developmental research for practice. New York, NY: Guilford Publications, 2013.
- 6 Ermisch J, Jantti M, Smeeding TM, eds. From parents to children: the intergenerational transmission of advantage. New York, NY: Russell Sage Foundation, 2012.
- 7 Marshall PJ, Kenney JW. Biological perspectives on the effects of early psychosocial experience. *Dev Rev* 2009; 29: 96–119.
- 8 Kolb B, Whishaw IQ. Fundamentals of human neuropsychology, 5th edn. New York, NY: Worth Publishers, 2003.
- Britto PR, Perez-Escamilla R. No second chances? Early critical periods in human development. Introduction. Soc Sci Med 2013; 97: 238–40.
- 10 Huttenlocher P. Neural plasticity: the effects of the environment on the development of the cerebral cortex. Cambridge, MA: Harvard University Press. 2002.
- 11 Ferguson KT, Cassells RC, MacAllister JW, Evans GW. The physical environment and child development: an international review. Int J Psychol 2013; 48: 437–68.
- 12 Walker SP, Wachs TD, Grantham-McGregor S, et al. Inequality in early childhood: risk and protective factors for early child development. *Lancet* 2011; 378: 1325–38.
- 13 LaFranchi SH. Approach to the diagnosis and treatment of neonatal hypothyroidism. J Clin Endocrinol Metab 2011; 96: 2959–67.
- 14 WHO. Proportion of births attended by a skilled health worker: 2008 updates. Geneva: World Health Organization, 2008.
- 15 Bradley RH, Putnick DL. Housing quality and access to material and learning resources within the home environment in developing countries. Child Dev 2012; 83: 76–91.
- 16 Wachs TD, Rahman A. The nature and impact of risk and protective influences on children's development in low-income countries. In: Britto PR, Engle PL, Super CM, eds. Handbook of early childhood development research and its impact on global policy. New York, NY: Oxford University Press, 2013: 85–122.
- Gertler P, Heckman J, Pinto R, et al. Labor market returns to an early childhood stimulation intervention in Jamaica. Science 2014; 344: 998–1001.
- 18 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.
- 19 Grantham-McGregor SM, Walker SP, Chang SM, Powell CA. Effects of early childhood supplementation with and without stimulation on later development in stunted Jamaican children. Am J Clin Nutr 1997; 66: 247–53.
- Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. *Lancet* 2014; 384: 1282–93.
- 21 Kagitcibasi C, Sunar D, Bekman S, Baydar N, Cemalcilar Z. Continuing effects of early enrichment in adult life: the Turkish Early Enrichment Project 22 years later. J Appl Dev Psychol 2009; 30: 764–79.
- 22 Kagitcibasi C, Sunar D, Bekman S. Long-term effects of early intervention: Turkish low-income mothers and children. J Appl Dev Psychol 2001; 22: 333–61.
- 23 Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions, version 5.1.0 (updated March, 2011). The Cochrane Collaboration, 2011.
- 24 Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; 387: 475–90.

- 25 Bhutta ZA, Das JK, Bahl R, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet* 2014; 384: 347–70.
- 26 Bhutta ZA, Das JK, Rizvi A, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 2013: 382: 452–77.
- 27 Bhutta ZA, Das JK, Walker N, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013; 381: 1417–29.
- 28 Lassi ZS, Kumar R, Mansoor T, Salam RA, Das JK, Bhutta ZA. Essential interventions: implementation strategies and proposed packages of care. Reprod Health 2014; 11 (suppl 1): S5.
- 29 The Partnership for Maternal, Newborn and Child Health. A global review of the key interventions related to reproductive, maternal, newborn and child health (RMNCH). Geneva: The Partnership for Maternal Health, Newborn and Child Health and the Aga Khan University. 2011.
- 30 Engle PL, Fernald LC, Alderman H, et al. Strategies for reducing inequalities and improving developmental outcomes for young children in low-income and middle-income countries. *Lancet* 2011; 378: 1339–53.
- 31 Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol 2015; 66: 433–57.
- 32 Rao N, Sun J, Wong JMS, et al. Early childhood development and cognitive development in developing countries: a rigorous literature review. London: Department for International Development, 2014.
- 33 Brown TW, van Urk FC, Waller R, Mayo-Wilson E. Centre-based day care for children younger than five years of age in low- and middleincome countries. Cochrane Database Syst Rev 2014; 4: CD010543.
- 34 Macmillan HL, Wathen CN, Barlow J, Fergusson DM, Leventhal JM, Taussig HN. Interventions to prevent child maltreatment and associated impairment. *Lancet* 2009; 373: 250–66.
- 35 Mikton C, Butchart A. Child maltreatment prevention: a systematic review of reviews. Bull World Health Organ 2009; 87: 353–61.
- 36 Britto PR, Ponguta LA, Reyes C, Karnati R. A systematic review of parenting programs for young children. New York, NY: United Nations Children's Emergency Fund, 2015.
- 37 Peacock S, Konrad S, Watson E, Nickel D, Muhajarine N. Effectiveness of home visiting programs on child outcomes: a systematic review. BMC Public Health 2013; 13: 17.
- 38 Segal L, Sara Opie R, Dalziel K. Theory! The missing link in understanding the performance of neonate/infant home-visiting programs to prevent child maltreatment: a systematic review. Milbank Q 2012; 90: 47–106.
- 39 Avellar SA, Supplee LH. Effectiveness of home visiting in improving child health and reducing child maltreatment. *Pediatrics* 2013; 132 (suppl 2): S90–99.
- 40 Knerr W, Gardner F, Cluver L. Improving positive parenting skills and reducing harsh and abusive parenting in low- and middle-income countries: a systematic review. Prev Sci 2013; 14: 352–63.
- Chen M, Chan KL. Effects of parenting programs on child maltreatment prevention: a meta-analysis. *Trauma Violence Abuse* 2016: 17: 88–104.
- 42 Topping KJ, Barron IG. School-based child sexual abuse prevention programs: a review of effectiveness. Rev Educ Res 2009; 79: 431–63.
- Walsh K, Zwi K, Woolfenden S, Shlonsky A. School-based education programmes for the prevention of child sexual abuse. Cochrane Database SystRev 2015; 4: CD004380.
- 44 Poole MK, Seal DW, Taylor CA. A systematic review of universal campaigns targeting child physical abuse prevention. *Health Educ Res* 2014; 29: 388–432.
- 45 Selph SS, Bougatsos C, Blazina I, Nelson HD. Behavioral interventions and counseling to prevent child abuse and neglect: a systematic review to update the US Preventive services task force recommendation. Ann Intern Med 2013; 158: 179–90.
- 46 Bailhache M, Leroy V, Pillet P, Salmi LR. Is early detection of abused children possible? A systematic review of the diagnostic accuracy of the identification of abused children. BMC Pediatr 2013; 13: 202.
- 47 Cummings M, Berkowitz SJ. Evaluation and treatment of childhood physical abuse and neglect: a review. Curr Psychiatry Rep 2014; 16: 429.
- 48 Schwartz KA, Preer G, McKeag H, Newton AW. Child maltreatment: a review of key literature in 2013. Curr Opin Pediatr 2014; 26: 396–404.

- 49 Lane WG. Prevention of child maltreatment. Pediatr Clin North Am 2014: 61: 873–88.
- 50 Manley J, Gitter S, Slavchevska V. How effective are cash transfers at improving nutritional status? World Dev 2013; 48: 133–55.
- 51 Bassani DG, Arora P, Wazny K, Gaffey MF, Lenters L, Bhutta ZA. Financial incentives and coverage of child health interventions: a systematic review and meta-analysis. BMC Public Health 2013; 13 (suppl 3): S30.
- 52 Fernald LCH, Gertler PJ, Hidrobo M. Conditional cash transfer programs: effects on growth, health and development in young children. In: King RB, Maholmes V, eds. The Oxford handbook of poverty and child development. Oxford: Oxford University Press, 2012.
- 53 Glassman A, Duran D, Koblinsky M. Impact of conditional cash transfers on maternal and newborn health. Washington, DC: Center for Global Development, 2013. http://www.cgdev.org/publication/ impact-conditional-cash (accessed June 1, 2015).
- 54 Ruel MT, Alderman H, Group MaCNS. Nutrition-sensitive interventions and programmes: how can they help to accelerate progress in improving maternal and child nutrition? *Lancet* 2013; 382: 536–51.
- 55 Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009; 62: 1013–20.
- 56 Zimmermann MB. The effects of iodine deficiency in pregnancy and infancy. Paediatr Perinat Epidemiol 2012; 26 (suppl 1): 108–17.
- 57 Roberts D, Dalziel Stuart R. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006; 3: CD004454.
- 58 Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev 2009; 1: CD004661.
- 59 Duley L, Henderson-Smart D, Meher S, King J. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007; 2: CD004659.
- 60 Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2013; 1: CD003311.
- 61 McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 2013; 7: CD004074.
- 62 Andersson O, Domellöf M, Andersson D, Hellström-Westas L. Effect of delayed cord clamping on neurodevelopment and infection at four months of age: a randomised trial. *Acta Paediatr* 2013; 102: 525–31.
- 63 Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev 2013; 10: CD001055.
- 64 Wang Y, Fu W, Liu J. Neurodevelopment in children with intrauterine growth restriction: adverse effects and interventions. J Matern Fetal Neonatal Med 2016; 29: 1–9.
- 65 Walker SP, Chang SM, Wright A, Osmond C, Grantham-McGregor SM. Early childhood stunting is associated with lower developmental levels in the subsequent generation of children. J Nutr 2015; 145: 823–28.
- 66 Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation. Paediatr Perinat Epidemiol 2012; 26 (suppl 1): 178–90.
- Haider B, Bhutta Z. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2015;
 11: CD004905.
- 68 Peña-Rosas JP, De-Regil Luz M, Garcia-Casal Maria N, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2015; 7: CD004736
- 69 Imdad A, Yakoob MY, Bhutta ZA. The effect of folic acid, protein energy and multiple micronutrient supplements in pregnancy on stillbirths. BMC Public Health 2011; 11 (suppl 3): S4.
- 70 Barrett J, Fleming AS. Annual Research Review: all mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. J Child Psychol Psychiatry 2011; 52: 368–97.
- 71 Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. *Lancet* 2014; 384: 1800–19.

- 72 Kvalevaag AL, Ramchandani PG, Hove O, Assmus J, Eberhard-Gran M, Biringer E. Paternal mental health and socioemotional and behavioral development in their children. Pediatrics 2013; 131: e463–69.
- 73 Rahman A, Fisher J, Bower P, et al. Interventions for common perinatal mental disorders in women in low-and middle-income countries: a systematic review and meta-analysis. Bull World Health Organ 2013; 91: 593–6011.
- 74 Ross LE, Grigoriadis S, Mamisashvili L, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry* 2013; 70: 436–43.
- 75 Huang H, Coleman S, Bridge JA, Yonkers K, Katon W. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. Gen Hosp Psychiatry 2014; 36: 13–18.
- 76 Singla DR, Kumbakumba E, Aboud FE. Effects of a parenting intervention to address both maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster-randomised trial. Lancet Glob Health 2015; 3: e458–69.
- 77 Aboud FE, Singla DR, Nahil MI, Borisova I. Effectiveness of a parenting program in Bangladesh to address early childhood health, growth and development. Soc Sci Med 2013; 97: 250–58.
- 78 Hodnett ED, Gates S, Hofmeyr GJ, Sakala C. Continuous support for women during childbirth. Cochrane Database Syst Rev 2013; 7: CD003766.
- 79 Powell C. An evaluation of the Roving Caregivers Programme of the Rural Family Support Organization, May Pen, Clarendon, Jamaica. Kingston, Jamaica: United Nations Population Fund, 2004.
- 80 Peairson S, Berghout Austin AM, de Aquino CN, de Burro EU. Cognitive development and home environment of rural Paraguayan infants and toddlers participation in Pastoral del Niño, an early child development program. J Res Child Educ 2008; 22: 343–62.
- 81 Hamadani JD, Huda SN, Khatun F, Grantham-McGregor SM. Psychosocial stimulation improves the development of undernourished children in rural Bangladesh. J Nutr 2006; 136: 2645–52.
- 82 Eickmann SH, Lima AC, Guerra MQ, et al. Improved cognitive and motor development in a community-based intervention of psychosocial stimulation in northeast Brazil. Dev Med Child Neurol 2003; 45: 536–41.
- 83 Panter-Brick C, Burgess A, Eggerman M, McAllister F, Pruett K, Leckman JF. Practitioner review: engaging fathers—recommendations for a game change in parenting interventions based on a systematic review of the global evidence. J Child Psychol Psychiatry 2014; 55: 1187–212.
- 84 Joseph S, Lonstein J, Levy F, Fleming AS. Common and divergent psychobiological mechanisms underlying maternal behaviors in non-human and human mammals. *Horm Behav* 2015: 73: 156–85.
- 85 Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev 2014; 4: CD002771.
- 86 Goldsmith F, O'Sullivan A, Smilowitz JT, Freeman SL. Lactation and intestinal microbiota: how early diet shapes the infant gut. J Mammary Gland Biol Neoplasia 2015; 20: 149–58.
- 87 Horta BL, de Mola CL, Victora CG. Breastfeeding and intelligence: a systematic review and meta-analysis. Acta Paediatr 2015; 104: 14-19
- 88 Victora CG, Horta BL, de Mola CL, et al. Association between breastfeeding and intelligence, educational attainment, and income at 30 years of age: a prospective birth cohort study from Brazil. *Lancet Glob Health* 2015; 3: e199–205.
- 89 Kramer MS, Aboud F, Mironova E, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry 2008; 65: 578–84.
- 90 Rochat TJ, Houle B, Stein A, et al. Exclusive breastfeeding and cognition, executive function and behavioural disorders in primary school-aged children in rural South Africa: a cohort analysis. PLoS Med 2016; 13: 1–51.
- 91 Eilander A, Gera T, Sachdev HS, et al. Multiple micronutrient supplementation for improving cognitive performance in children: systematic review of randomized controlled trials. *Am J Clin Nutr* 2009; 91: 115–30.

- 92 De-Regil LM, Jefferds MED, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database Syst Rev 2011; 12: CD009085.
- 93 Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. *Public Health Nutr* 2005; 8: 117–32.
- 64 Kristjansson E, Francis DK, Liberato S, et al. Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years. Cochrane Database Syst Rev 2015; 3: CD009924.
- 95 Aboud FE, Moore AC, Akhter S. Effectiveness of a community-based responsive feeding programme in rural Bangladesh: a cluster randomized field trial. *Matern Child Nutr* 2008; 4: 275–86.
- 96 Vazir S, Engle P, Balakrishna N, et al. Cluster-randomized trial on complementary and responsive feeding education to caregivers found improved dietary intake, growth and development among rural Indian toddlers. Matern Child Nutr 2013; 9: 99–117.
- 97 Teicher MH, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am J Psychiatry 2013; 170: 1114–33.
- 98 Bick J, Zhu T, Stamoulis C, Fox NA, Zeanah C, Nelson CA. Effect of early institutionalization and foster care on long-term white matter development: a randomized clinical trial. *JAMA Pediatr* 2015; 169: 211–19.
- 99 Lomanowska AM, Boivin M, Hertzman C, Fleming AS. Parenting begets parenting: A neurobiological perspective on early adversity and the transmission of parenting styles across generations. *Neuroscience* 2015; published online Sept 16. DOI:10.1016/j.neuroscience.2015.09.029.
- 100 Prinz RJ, Sanders MR, Shapiro CJ, Whitaker DJ, Lutzker JR. Population-based prevention of child maltreatment: the US Triple P system population trial. Prev Sci 2009; 10: 1–12.
- 101 Rao N, Sun J, Pearson V, et al. Is something better than nothing? An evaluation of early childhood programs in Cambodia. *Child Dev* 2012; 83: 864–76.
- 102 Mundy K, Proulx K, Janigan K, Geva E, Fraser C. Evaluation of the Child-to-Child school readiness programme in Ethiopia. Addis Ababa: United Nations Educational, Scientific and Cultural Organization, 2014.
- 103 Leyva D, Weiland C, Barata M, et al. Teacher-child interactions in Chile and their associations with prekindergarten outcomes. Child Dev 2015; 86: 781–99.
- 104 Araujo M, Carneiro P, Cruz-Aguayo Y, Schady N. A helping hand? Teacher quality and learning outcomes in kindergarten. Washington, DC: Inter-American Development Bank, 2014.
- 105 Attanasio OP, Fernandez C, Fitzsimons EO, Grantham-McGregor SM, Meghir C, Rubio-Codina M. Using the infrastructure of a conditional cash transfer program to deliver a scalable integrated early child development program in Colombia: cluster randomized controlled trial. BMJ 2014; 349: g5785.
- 106 Fernald LCH, Kagawa RMC, Knauer HA, Garcia Guerra A, Schnaas L, Neufeld LM. Promoting child development through group-based parent support within a cash transfer program: experimental effects on children's outcomes. *Dev Psychol* (in press).
- 107 Denboba A, Sayre R, Wodon Q, Elder L, Rawlings L, Lombardi J. Investing in young children: key interventions and principles to ensure all young children reach their full potential. Washington, DC: World Bank Group, 2014.
- 108 Richter LM, Daelmans B, Lombardi J, et al, with the Paper 3 Working Group, for the Lancet Early Childhood Development Series Steering Committee. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. Lancet 2016; published online Oct 4. http://dx.doi.org/10.1016/ S0140-6736(16)31698-1.
- 109 Birn RM, Patriat R, Phillips ML, Germain A, Herringa RJ. Childhood maltreatment and combat posttraumatic stress differentially predict fear-related fronto-subcortical connectivity. Depress Anxiety 2014 Oct; 31: 880–92.
- 110 Campbell JA, Walker RJ, Egede LE. Associations between adverse childhood experiences, high-risk behaviors, and morbidity in adulthood. Am J Prev Med 2015; 50: 344–52.