

# Annual Review of Nutrition The Nexus Between Nutrition and Early Childhood Development

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cognitive development, child stimulation, integrated nutrition programs

#### Abstract

This article looks at both nutrition and early childhood stimulation interventions as part of an integrated life cycle approach to development. We build on recent systematic reviews of child development, which are comprehensive in regard to what is currently known about outcomes reported in key studies. We then focus particularly on implementation, scaling, and economic returns, drawing mainly on experience in low- and middle-income countries where undernutrition and poor child development remain significant public health challenges with implications across the life course.

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#### **1. NUTRITION IN AN ERA OF DECLINING CHILD MORTALITY**

Physical growth is intrinsically linked with cognitive and socio-emotional development and shares many of the same risk factors and protective measures (27). The well-known UNICEF conceptual framework for nutritional outcomes includes care as one of three underlying causes of malnutrition (28). The 2013 *Lancet* series on nutrition modifies that model and indicates that the outcomes of optimal fetal and child nutrition include learning capacity and emotional development as well as



Conceptual representation of nurturing care.

outcomes such as physical stature and overweight or obesity (29). Nurturing care is an extension of this model and has been highlighted as a focal point of the recent *Lancet* series on early childhood development (ECD) (**Figure 1**).

Nurturing care is described as a prime determinant of a child's physical and psychological development (33). This concept is characterized by having a stable home environment that is sensitive to children's health and nutritional needs, responsive, emotionally supportive, and developmentally stimulating, with opportunities for play and exploration and protection from adversities. With the recent decline of nutrition-related child mortality—as has recently been the case globally cognitive and emotional development are even more relevant as outcomes and goals of nutrition interventions. Furthermore, significant long-term effects of better ECD translate into lifelong benefits such as labor market participation and earnings (109).

The distinction, then, between programs or interventions focusing on improving nutritional inputs (e.g., through provision of vitamin A, protein, iron) and those promoting ECD (e.g., through parenting support or improving access to daycare) is not always clear (**Figure 2**). For example, the provision of adequate food and nutrients, which is easily considered the domain of nutrition, includes interventions such as iodine fortification for which cognitive development as well as mortality reduction is the main outcome of interest. Similarly, other fortification and supplementation programs (e.g., support of complementary feeding) are aimed as much at improving cognition as at improving stature. Despite this growing acknowledgment of the importance of cognitive development, the six World Health Assembly 2025 targets for nutrition are presented in terms of optimal physical growth: (*a*) achieve a 40% reduction in the number of children under 5 who are stunted, (*b*) achieve a 50% reduction of anemia in women of reproductive age, (*c*) achieve a 30% reduction in low birth weight, (*d*) ensure there is no increase in childhood overweight, (*e*) increase the rate of exclusive breastfeeding in the first 6 months by at least 50%, and (*f*) reduce and maintain childhood wasting at less than 5%. These targets do not include



Examples of inputs that affect physical growth, developmental outcomes, or both.

increased cognitive capacity, which remains in another domain (137). Stunting and extreme poverty often serve as proxy measures for child development because they are associated with children's cognitive and physical development, are measured globally using uniform methods, and are responsive to environmental and economic changes (27).

This article looks at both nutrition and early childhood stimulation interventions as part of an integrated life cycle approach to development. We build on recent systematic reviews of child development (3, 33, 42, 62). These reviews are comprehensive in regard to what is currently known about outcomes reported in key studies. To augment this information, we focus particularly on implementation, scaling, and economic returns, drawing mainly on experience in low- and middleincome countries where undernutrition remains a public health challenge. Although there is also an awareness of overweight and obesity in these populations, we do not focus on these issues.

Specifically, we begin by presenting a conceptualization of investment in child development over time (Section 2) in which we discuss underlying issues relating to nutrition and cognitive development, including evidence pertaining to breastfeeding, complementary feeding, growth faltering, and micronutrients. We then present some evidence from longitudinal data in which it is occasionally possible to tease out the plasticity and the timing of responses over stages in the life cycle and thus fine-tune the understanding of critical periods for intervention studies (Section 3). In Section 4, we examine a subset of programs that by design combine the delivery of nutrition services and child stimulation as a core component of this review. In Section 5 we discuss the implications of our findings for priorities in nutrition and ECD.

#### 2. CONCEPTUALIZING INVESTMENTS IN CHILD DEVELOPMENT OVER TIME

#### 2.1. Underlying Contributors to Nutrition and Cognitive/Socio-Emotional Development

Children growing up in poverty may not receive the appropriate care, stimulation, or nutrition required to promote optimal development. They are often exposed to concurrent risk factors that



Interventions, risks, and protective factors influencing development across the life course. Figure created by Elizabeth Prado and inspired by Reference 136.

can interfere with the developmental process within the first years of life (27). Extreme poverty increases food insecurity, poor sanitation or hygiene, child abuse, and neglect, and these accumulated adversities can have potent negative effects on development (46). Interventions reducing risk factors or enhancing protective factors can have a beneficial effect on the trajectory of child development (**Figure 3**). The promotion of nurturing care through the home environment may attenuate the effects of poverty (30, 78, 81).

#### 2.2. Central Role of Breastfeeding

Nurturing care includes the early initiation of breastfeeding, regular and responsive feeding, exclusive breastfeeding for the first 6 months of life, and continued breastfeeding through the first 2 years of life (33). Promotion of exclusive breastfeeding, including the provision of colostrum in the first few hours and days of a baby's life, is one of the most widely supported interventions for nutrition (26). Convincing meta-analysis presents evidence of the importance of breastfeeding for child survival, with new data supporting the unique biological contribution to the child's immune response (131). Ethics and logistics make randomized trials of breastfeeding impossible, yet systematic reviews have found evidence based on observational studies that indicate an average contribution of breastfeeding to subsequent IQ of over 2.6 points in low- and middle-income countries. Although the effect size is small, the scale of this practice implies a significant aggregate economic loss from shortened breastfeeding; the loss was estimated at \$302 billion for 2012 (110). Despite these critically important links between breastfeeding and improved cognitive outcomes, systematic reviews of the effects of breastfeeding did not find a direct contribution of breastfeeding to length or weight in children under 6 months of age (26). This, again, is consistent with the framework for actions in nutrition and child development (29), which places cognitive development and improved stature on the same level of desired outcomes.

A mother may not be able to breastfeed because of time constraints, maternal depression (18), lack of family support, and inability to breastfeed while working, among other reasons. As the International Code of Marketing of Breastmilk Substitutes is evaded in many settings, mothers are also often persuaded that their breastmilk cannot provide the same nutrition for their child as offered by substitutes. From the perspective of this review, there are numerous examples of successful prenatal and postnatal behavioral change interventions that improve breastfeeding practices despite the challenges of encouraging such change in the face of complex family obligations and labor constraints (67). Such communications—similar to other programs to enhance a range of parenting skills—lead on average to a 43% increase of breastfeeding at day 1 as well as increased breastfeeding at 1–4 months after birth.

#### 2.3. Critical Role of Complementary Feeding from 6 to 24 Months

The period of complementary feeding corresponds directly with the timing of growth faltering from 6 to 24 months. Interventions to address complementary feeding are successful only when they involve intensive counseling and strongly emphasize dietary diversity and the promotion and consumption of animal source foods (45). For example, two programs [one in Peru (98) and the other in China (64)] demonstrate that primary caregivers are able to act on the advice of community nutrition workers to provide higher-quality, micronutrient-rich, complementary foods. Similarly, visits to low-income Malawian homes that included nutritional information from birth to the first year of life contributed to significant improvements in the consumption of protein-rich foods and in height-for-age z-scores (HAZ) (55). Likewise, intensive promotion of diet diversity in Bangladesh advanced language and gross motor skills in children aged 6–24 months (56).

Lipid-based nutrient supplements (LNS), which include micronutrients, protein, and essential fatty acids, have been evaluated in a number of settings (5, 6, 15, 23, 44, 68, 88, 105, 113). LNS products have been developed to treat moderate or severe malnutrition and prevent child stunting. Evidence from a number of efficacy trials in Africa and Asia suggests that LNS products have small but significant benefits for infant growth and development (4, 99, 100, 101, 103). Although these data are mixed, subgroup analyses suggest that benefits are greatest among those with higher food insecurity.

# 2.4. Association Between Stunting and Cognitive/Language Development Outcomes

Children's early development is characterized by sensitive periods for skill development related to maturation and genetic-environment interactions, and the impact of interventions varies with timing and environmental conditions (27). The neurobiological foundation of child development, however, is largely beyond the scope of this article, which focuses on programmatic synergies. We do, nonetheless, present a schematic representation of critical periods and important periods of development for both cognitive development and linear growth from conception through adolescence (**Figure 4**).

Stunting is commonly considered to be irreversible after the age of 2 or 3 (130), although this finding is controversial and discussed in greater detail in Section 3. Stunting is associated with cognitive and language development by means of common factors that influence both such as poverty. These associations between stature and cognition are bolstered by the extensive body of research elucidating the biological mechanisms underlying results from cross-sectional and prospective studies (102). A meta-analysis of 68 studies from 29 low- and middle-income countries found that HAZ and cognition were positively associated in children under 2 years of age; there were also associations of a similar magnitude between HAZ and cognition at 5–11 years of age (120). Height was also associated with motor development, but there were too few studies to examine the associations between height and socio-emotional development.



Critical and important periods for linear growth and child development. The first 1,000 days are considered a critical period for growth because most stunting occurs due to prenatal and early-life insults, but there may be the potential to catch up in height relative to peers later in childhood (indicated by the lighter colored bar in adolescence). Darker colors represent critical periods for growth and development; lighter colors are important periods and represent opportunities for interventions. Information presented in the figure is from Reference 124.

As presented recently in the Lancet series on ECD (27, 33, 109) and discussed further below, there is a growing body of research on programs that have the potential to improve cognitive and socio-emotional development after age 2. In partial contrast, despite the likelihood that some catch-up growth occurs after age 2, there is little evidence or experience about which public health interventions can effectively influence linear growth after a child's second birthday (104). Moreover, linear growth, even if it responds to programs, might be deemphasized after age 2, because weight gain on small frames has been associated with subsequent obesity and adult chronic diseases (86, 128), whereas there are no analogous risks from stimulation.

#### 2.5. Proximal and Distal Causes of Poor Development and Growth

Programs targeting nutrition can be classified as nutrition-specific interventions (i.e., those that address the immediate determinants of nutrition, such as inadequate nutrient intake and poor caregiving practices) or nutrition-sensitive interventions (i.e., those that address the underlying causes of undernutrition, such as poverty, food insecurity, or scarcity of water and sanitation services) (111). Some programs that are nutrition sensitive lead to improvements in both physical growth and cognitive development (33). Although some programs such as conditional cash transfers (CCTs) have positive effects on child health outcomes (20), the effects on child height and weight are mixed (84). A few evaluations have examined the effects of CCTs on development in young children and most report significant but small positive effects on cognitive and language development (19, 48–50, 82, 97), as well as significant benefits for child behavior (49, 94). For example, a CCT program in Nicaragua increased cognitive measures and achieved small improvements in HAZ (83). Conversely, a CCT program in Peru did not show any improvement in vocabulary or grade attainment, although it did lead to increased HAZ among boys (14). These inconsistent findings on CCT programs are not surprising given the diverse packages of interventions encouraged by CCTs and the broad age coverage of the evaluations (11).

#### 2.6. Association Between Micronutrients and Development Outcomes

Various nutrients and interventions promote healthy brain development often in the context of linear growth, and effects vary with the timing, dose, and duration of access and deficiencies (59). Nutritional deficiencies prior to conception and during pregnancy can result in neural tube disorders, low birth weight and length, and lifelong negative consequences, including developmental delays/disabilities (25). Only a subset of trials of nutrition-specific interventions have observed cognitive as well as anthropometric measures.

Fortification of commonly consumed foods (e.g., salt, sugar, fish sauce) is one response to inadequate micronutrient intake—and one means of verifying the causal pathways from deficiency to developmental delays. Iodine fortification of salt, for example, is widespread and particularly important for pregnant women and young children. A systematic review including observational studies has found that iodine-deficient populations are 12–13.5 IQ points lower than replete communities (140). The review also indicates that iodized oil supplements have a similar impact as salt fortification, albeit at higher costs; despite the costs, however, iodized oil may be advised in settings where iodine deficiency is endemic. These examples indicate the inseparable tie between nutrition-specific interventions and cognitive outcomes. However, because these interventions are based on fortification and supplementation, they do not require sectoral integration to achieve their results.

In partial contrast to the evidence for iodine, the pattern of age response to iron supplementation is less clear. Britto et al. (33) do not list prenatal iron supplements as improving child development and present conflicting evidence for supplementation in school-aged children. Although evidence indicates that iron supplementation in children less than 2 years of age reduces anemia, a meta-analysis of iron supplementation found no convincing evidence that supplements for children under 27 months effectively improve mental development. However, that review also noted that supplements for children older than 7 years of age do improve intelligence, particularly for children who initially had iron deficiency anemia (112). A more recent systematic review focusing only on children under 24 months reiterated the uncertain impacts of iron supplementation on development (96). Further, a longitudinal study showed that Nepalese children 7–9 years of age who received iron-folate or zinc supplementation when 12–35 months old did not have improved intellectual or executive performance (89).

Micronutrient interventions also provide evidence for intergenerational effects of nutrition interventions. For example, a recent study examined at a programmatic scale the rollout of oil capsule supplementation in Tanzania and noted a subsequent increase in schooling of the next generation compared with children of women not yet in the program, with the benefits accruing mainly to adolescent girls (53). Similar results were found for Ethiopian migrants in Israel (77). As with the Tanzanian study, this result was driven almost exclusively by the impact on girls.

Despite some promising examples of prenatal iron supplementation, the overall evidence for intergenerational effects is mixed as it is for other age brackets (43). For example, Nepalese children 7–9 years of age whose mothers received iron-folate supplements during pregnancy but who did not

receive supplements in preschool exhibited at age 7 improvements in working memory, inhibitory control, and fine motor function (37). This result, however, was not found in a similar longitudinal study in China that compared a multiple micronutrient supplement that included iron with folate alone (79).

### 3. CATCH-UP GROWTH, CATCH-UP DEVELOPMENT, AND TIMING OF PROGRAMS

#### 3.1. Timing of Stunting and Catch-Up Growth

In the past decade, priorities in nutrition have been strongly influenced by the view summarized by Victora et al. (130, p. 340): "Poor fetal growth or stunting in the first 2 years of life leads to *irreversible* damage, including shorter adult height, lower attained schooling, reduced adult income, and decreased offspring birthweight" [italics added]. Most stunting occurs due to prenatal and early-life insults; this conclusion is not debated among nutritionists. However, there is some dispute about whether a child who becomes stunted during the first 2 years of life has appreciable potential to catch up in height relative to peers later in childhood (104, 115). For example, studies using the Young Lives data (a longitudinal set of cohort surveys in Ethiopia, Andhra Pradesh state in India, the Philippines, and Vietnam with approximately 2,000 children born in 2001 per country sample) indicate that some stunted children improve as they age even without any major changes in the economic or environmental conditions of the area in which the child resides. This series of surveys, however, conducted rounds at 1, 5, and 8 years of age and thus is not designed to pinpoint sensitive periods with precision. Analyses of the Young Lives data are described in greater detail in the next section.

#### 3.2. Early-Life Investments Versus Later-Life Investments

A range of investments have the potential to promote nutritional status and cognitive development within the context of nurturing care (**Figure 5**). As depicted in the figure, optimal child development is defined as improved cognition and motor and socio-emotional development, in addition to improved school performance, learning, work capacity, and productivity. These outcomes are directly affected by four key categories of inputs (health, nutrition, caregiving, and education) via direct biological benefits of micro- and macronutrients and decreased disease burden and psychological benefits of exposure to a stimulating and supportive home environment and opportunities for learning outside the home. These inputs are supported by enabling environments for the caregiver, in addition to larger social, economic, political, and contextual factors.

There are clear implications of the timing of stunting and how it affects our conceptualization of the nexus between nutrition and broader child development. As with linear growth, the early years in a child's life are critical for cognitive and socio-emotional development, with opportunities as well as challenges that can be difficult, if not impossible, to overcome. For example, the association between linear growth and cognitive development is stronger for children under 2 years of age than for older children, although the association does appear to persist beyond the first 2 years of a child's life (120).

Moreover, changes in height over time are associated with improvements in cognition; recent studies provide some insight into the time in which gains in nutrition might be associated with other improvements in development. For example, analyses of the Young Lives study indicate that children who catch up in stature later in childhood from early episodes of stunting have cognitive scores similar to those who never experienced growth faltering; in particular, both stature at age 1





Proximate and distal factors that are critical and important for promoting optimal child development. Figure inspired by Reference 27. Abbreviation: CCT, conditional cash transfer.

and later growth that is not predicted by that earlier stature were positively associated with math and reading at age 8 (39). The improvements in the later rounds of the Young Lives data appear to be due partly to parental investments in response to health and weather shocks (58).

The rounds of the Young Lives Surveys that covered changes in stature between ages 8 and 15 presented evidence of the relationship between improved stature and cognitive development (54). Similarly, a prospective study comparing growth of Malawian children between 1 and 24 months and between 2 and 15 years of age found that the latter period but not the former was associated with performance on Raven's matrices (123). An additional cohort study from urban South Africa found that children who had been stunted prior to age 2 but who had recovered by age 5 performed better on the Denver Developmental Screening Test than children who had not recovered (34). Nevertheless, this recovery was only partial; even children who had improved performed relatively poorly on the test compared with children who had never been stunted.

A study that tracked children in Bangladesh from birth through 64 months found that growth in length as well as weight during the first 2 years had larger effects on IQ than did later growth (66). In partial contrast, one observational panel study using the Young Lives data in Peru found that stunting at ages 4.5–6 was more strongly associated with vocabulary than earlier stunting was. Stunting in either age bracket was associated with cognitive development, with no significant

difference between the two associations (38). The authors' inference that interventions preventing linear growth faltering should focus not only on children under 2 years but also on children up to 5 years of age is, however, premature because the cost-effectiveness of interventions to address stunting at either age is not indicated. Moreover, the relative effectiveness of interventions to affect cognitive development that do not aim to influence stunting also needs to be considered in drawing this conclusion. Indeed, as Aboud & Yousafzai (3) indicate in a meta-analysis, the effect size of nutrition interventions on cognitive outcomes is far smaller than the effect size of enhanced stimulation, although the relative costs of achieving these results were not indicated.

#### 3.3. Economic Models for Conceptualizing Investments Across the Life Course

Economic models of adult capacities (physical, cognitive, socio-emotional, executive function) view these as outcomes of investments in the life course (7, 9, 40). This approach incorporates the possibility of early inputs fading out in subsequent periods or, alternatively, amplifying over time, and provides a basis for understanding the need for comprehensive programs that transition over stages in a child's development. One concept in this framework is self-productivity, which indicates that better health (or skills) in one period creates even higher levels of health (skills) later. Another concept in such models is that of dynamic complementarities. If these are present, then better health (skills) in one period could lead to greater returns on subsequent investments including schooling. Alternatively, there could be dynamic substitutes, such that programs in a later period can offset earlier disparities. For example, children with limited opportunities in their home environments may benefit from preschool programs more than other children would (13). Thus, these programs can partially substitute for limited inputs at home.

This framework helps us understand how short-term health shocks may affect future outcomes. If self-productivity and dynamic complementarities are strong, then moderately sized shocks to health in early life might lead to major differences in schooling outcomes thereafter (69). Moreover, if there are dynamic complementarities, then successful investments in skills development in one period may establish a platform for the achievement of a later program. For example, a subset of girls who were randomly selected to participate in the Abecedarian Project benefited from a later school program, whereas a subset of girls from the initial control did not (74). Complementarity, then, reinforces the understanding of the value of early investments. Substitution, in contrast, opens up the possibility that shocks can be reversed or mitigated after the event.

An important inference of dynamic complementarities is that from an economic efficiency perspective, both public and private investments should be targeted to those with better initial health and greater skills, although this would widen disparities in the population as children age. However, if there are dynamic substitutes, then it is economically efficient to direct investments toward children with poorer health to compensate for limited prior investments. Such targeting also improves equity and may be a motive for government programs even when there are efficiency costs.

Thus, better knowledge of current and interperiod substitution would help researchers design programs to reduce these gaps and to assess the relative costs of preventing rather than alleviating these gaps. We turn to this in the next section.

# 4. EFFECTS OF INTEGRATED NUTRITION–STIMULATION INTERVENTIONS

#### 4.1. Types of Programs Supporting Child Development

Providing families with home visits or group-based curricula can improve outcomes for children living in poverty in both high-income (92) and low- and middle-income (33) countries. Parenting

interventions use home visits, primary health care visits, group sessions with caregivers, nutritional services, and combinations thereof to improve cognitive function and health in early childhood. Meta-analyses of parenting and home-visiting programs have found that the most effective parenting programs included systematic training methods; a structured, evidence-based curriculum; and opportunities for parental practice and feedback with children. These reviews also found that the quality of the relationship between parent and worker influenced effectiveness (87, 93, 122).

# 4.2. Considerations for Integrating Multiple Interventions to Promote Child Development

Integrated programs and packages with shared messages and opportunities for synergy are widely promoted (33). Support for integration stems from the perceived benefits of coordinating with the health and nutrition sectors, which are often the only services reaching children under 3 years of age (**Figure 5**). Possible disadvantages, however, are that routine health and nutrition services are often limited, few services are scheduled for children after 12 months, and many health and nutrition services are already overstretched, especially in the poorest countries.

Grantham-McGregor et al. (62) recently reviewed the effects of integrated programs and found relatively little evidence of synergy between stimulation and nutrition interventions in the small-scale programs and trials specifically designed to test this possibility; running both types of interventions jointly often leads to the same outcomes as running each type independently. Thus, integrated programs appear additive rather than synergistic. Although evidence supporting the benefits of integrated programs above and beyond the individual program components is lacking, the child development policy and advocacy community has shown interest in using integrated programs to incorporate the promotion of child development within a range of government sectors (33).

Nutrition interventions can occasionally have modest impacts on cognitive outcomes, but this pathway remains small and does not increase significantly when combined with enhanced stimulation (62). As with all measurements of interactions, this result can also be stated as the effect of stimulation on cognitive outcomes, although generally significant, does not increase further in the presence of feeding programs. Similarly, there are only a few examples of enhanced stimulation influencing linear growth. The absence of synergistic effects on cognitive outcomes in joint interventions is also the norm in regard to stimulation having little influence on the effects of nutrition interventions on growth and morbidity (62). Practically speaking, if there is no downside to designing joint programs, the value of such an implementation may depend on the costs of delivery. If it costs less to have joint management and some common infrastructure, then the costs to achieve a desired outcome would be reduced even if there is no additional impact.

### 4.3. Effects of Integrated Interventions and Programs at Scale on Child Growth and Development

A trial in Colombia (17) published after Grantham-McGregor et al.'s review (62) offered weekly stimulation with play demonstrations delivered by community members over a period of 18 months, micronutrient sprinkles given daily, or both. This program and study design was based on an earlier well-known study from Jamaica that has contributed extensively to the literature on the integration of stimulation and supplementation (63). However, the supplementation in the Colombian study consisted only of micronutrients whereas the Jamaica study provided a milk-based formula. Both studies found that stimulation led to improved cognitive development—and, in Colombia, improved receptive language—but neither trial found nutrition to affect cognitive outcomes.

Another study (51) published after Grantham-McGregor et al.'s review examined whether adding parenting education and a support program provided in a group setting to Mexico's CCT program could result in greater benefits for children than participating in a CCT program alone. This cluster-randomized effectiveness study found that children whose communities had been randomized to receive weekly group-based parenting support performed better on tests of child development than did children whose communities did not have such sessions. This finding held only for households in communities randomized to the arm in which group participation was integrated with the existing CCT program and encouraged and supported by the CCT. There were no differences in cognitive outcomes between children living in communities where the parenting program was not supported by the CCT program and children living in communities where the program was not available.

Further, a recent  $2 \times 2$  factorial study in Pakistan compared enhanced nutrition education plus micronutrient powders with responsive stimulation as well as with a combination (139). The program was conducted during monthly community sessions and home visits (139). Stimulation resulted in improved cognition, language, and motor development, with relatively large effect sizes of 0.6, 0.7, and 0.5, respectively, at 24 months of age. Scores on cognitive tests were lower at 24 months, however, than at 12 months in all arms of the study; moreover, no improvement of socio-emotional development was observed. Although enhanced nutrition led to a small improvement in linear growth, as well as improved language scores, but no improvement in the other two dimensions of development measured—unlike the general results in the meta-analysis reported above (62)—there was a significant negative effect of the joint intervention compared to stimulation alone. The micronutrient home supplementation also did not lead to changes in hemoglobin status.

One low-cost approach to linking parental training with health care was studied in the Caribbean. In this randomized controlled trial, films containing messages about child development were shown during 5 scheduled visits to health clinics over a 15-month period beginning in the child's third month (36). Community health workers who were part of the health care system were provided additional training to facilitate discussions of the films with the caregivers in the waiting areas. The program resulted in increased cognitive development (although not in the language domain) and maternal knowledge about child learning. As these messages were delivered during normal waiting times, the approach addresses a common obstacle to behavioral change communication: the additional burden on the caregiver's time. This approach benefited from the high turnout to scheduled visits that is the norm in the community, in partial contrast to many South Asian and African settings. This approach could prove more scalable and cost-effective than home visits, even though the latter are likely to achieve greater effect size improvements in cognitive measures.

Although not designed as a  $2 \times 2$  trial, analysis of daycare provided in Bolivia's Proyecto Integral de Desarrollo Infantil (PIDI) provides insight into the joint provisions of stimulation and food within the context of daycare (22). In this program, groups of as many as 15 children between the ages of 6 and 72 months were provided daycare in the homes of women in low-income neighborhoods. Controlling for selection as well as length of exposure, the study recorded improvements in measures of language and auditory development, psychosocial skills, and gross and fine motor development, but not height or weight.

The PIDI program was modeled after Colombia's publicly funded daycare program, Hogares Comunitarios de Bienestar, although the long-running program focuses on an older age group, starting at age 3 and continuing to age 6. Arguably, the age of entry can explain the result that children who had spent at least 15 months in the program did not show improvements in nutritional status, although they did improve in both cognitive development and socio-emotional skills (24).

Taken together, these studies support integrated interventions that rely on multiple sectors for the promotion of child development and that intervene with the family as a unit rather than the child alone. Furthermore, interventions can be improved by combining them with nurturing care and protection through parenting support and skills programs. In fact, one of the key conclusions from the recent *Lancet* (33) series on ECD is that child growth and development would be best supported through packages of interventions, such as the family support and strengthening package (which includes access to quality services, skill building, and social support), the multigenerational nurturing care package (which includes care and protection of the mother and father's physical and mental health and well-being), and the early learning and protection package (which includes support for young children with parental support and a nurturing environment in early childhood centers, classrooms, and community settings).

#### 4.4. Integrating Child Stimulation into Complementary Feeding Interventions

Responsive feeding interventions can integrate behavioral change education about complementary feeding and advice on how to feed a child. Thus, meal times may serve as an opportunity for child stimulation. Although studies of education on complementary feeding regularly show that education with or without the provision of complementary foods leads to increased linear growth (73) and efficacy trials of responsive feeding often find changes in maternal interaction and, less frequently, in cognitive outcomes (65), these studies are mixed in regard to synergy. For example, a trial in Bangladesh that included six sessions to encourage verbal interaction while feeding with or without micronutrient supplementation recorded improved language development of children and improved caregiver interaction in both variants of the treatment, as well as weight gain if, and only if, supplements were included. However, supplements did not enhance the effect of the responsive feeding (1).

Similarly, a trial in Andhra Pradesh, India, that combined a demonstration of responsive feeding as well as the provision of basic toys with a more conventional efficacy trial on counseling on complementary feeding during biweekly visits found that complementary feeding decreased stunting while only the responsive feeding arm led to increased mental development. However, the responsive feeding and stimulation arm did not improve nutritional indicators even though the services provided in the complementary feeding arm were embedded in the responsive feeding arm (129). The study speculated that the absence of a nutritional impact in the joint arm of the intervention might reflect information overload. The joint arm received more than twice as many behavioral change messages in the same number of visits as did the feeding arm. Given the time constraints of the caregiver and the complexity of these messages, the caregivers might not have been able to implement all recommendations.

Another trial, included in Reference 62, provided severely underweight children 6–24 months old in Bangladesh with psychosocial stimulation through home visits with or without modest food supplements upon discharge from the hospital. The intervention had an appreciable impact on cognitive development and a small impact on weight-for-age, but there were no synergistic effects (91). Subsequent analysis investigated whether the intervention affected symptoms of maternal depression; no significant effects on depressive symptoms were found (90).

# 4.5. Integrating Prevention of Maternal Depression with Nutrition Interventions

Maternal depression, or having a high maternal depressive symptoms score, usually means that a woman has somatic symptoms, a lack of positive affect, a depressive affect, and/or self-reported interpersonal programs. The concern with maternal depression is a question about outcomes and

risk factors for both undernutrition and delayed cognitive development. Thus, programs that can mitigate depression are intrinsically joint nutrition and development endeavors or, more precisely, a single intervention with multiple outcomes. Moreover, unlike many other programs, they address the woman as an individual and not merely as a caregiver.

A few programs have shown potential to address high depressive symptoms in the field, particularly in South Asia, with favorable impacts on birth outcomes (127). There is a clear observational association between maternal depressive symptoms and child development outcomes, as indicated in a meta-analysis of the risk for malnutrition in children of mothers demonstrating symptoms of depression (121). In these studies, depression was either assessed through standardized diagnostic interviews or based on depressive symptoms self-reported in a questionnaire, such as that used in the CES-D (Center for Epidemiological Studies-Depression) (121). However, the record on interventions affecting child development is less sanguine.

One study noted that community groups in Uganda were able to improve depressive symptoms in mothers and cognitive scores of children over 12 sessions but found no impacts on physical growth (117). Similarly, regular visits from community health workers in South Africa over a 36-month period resulted in less depression as well as less stunting and improved vocabulary (125, 126). However, another study in this vein from Pakistan was unable to find lasting impacts on the socio-emotional, cognitive, and physical development of children approximately 7 years of age whose mothers benefited from the program Thinking Healthy, which reduced postpartum depression for 12 months after delivery (85, 107).

Extreme stress early in life can have lifetime consequences (116). Anxiety caused by poverty is associated with stress that can affect fetal development. Short-term stress, for example, caused by disasters or warfare, can also influence growth in utero (33). A fetus is particularly sensitive to prenatal stress in the first trimester of pregnancy, partially through cortisol, with changes in the amygdala apparent when the child is 6 months old (106). However, prenatal stress may have an additional pathway affecting development that differs from postnatal depression (118); these findings are reviewed in the second paper of the three-paper *Lancet* series (33). A few key findings, based on a meta-analysis of 13 studies in primarily lower- and middle-income countries, were that effective interventions for mothers with depression included maternal support groups and infant massage (75). Also, group-based parenting programs can improve maternal mental health in community settings, as shown in recent studies in Bangladesh and Uganda (2, 117).

#### 4.6. Duration of Effects: Short Term, Long Term, or Lifetime?

To fully assess the impact of the programs reviewed here, we need to address the vexing evidence of fade-out. Numerous programs have shown promising initial results that dissipate over time. For example, food supplementation in the Jamaica crossover trial had a modest impact on physical growth initially as well as an additive impact of combined stimulation and nutrition. The impact on physical growth was no longer apparent by age 7 nor was the additive impact apparent (63, 135). Similarly, although daily maternal supplementation of 1,025 kcal and 22 g protein in the Gambia led to a relatively large increase in birthweights and significantly reduced infant mortality, the beneficiaries showed no improvement in cognitive or physical measures of development in late adolescence (10). In the Jamaica trial, the absence of lasting improvement in anthropometry was attributed to declining responsiveness as a child reaches his or her second birthday; in the Gambia study, the lack of lasting impact was explained by the absence of a sustained set of interventions addressing age-specific needs of the child (119). From the opposite perspective, the emergence of a cluster of benefits over three years with regular visits from community workers in South Africa was attributed to the continuing contact over the period (126).

A Malawi-based, cluster-randomized study of the effects of quality improvements on community-based childcare centers (CBCCs) found that children benefited in the short term (18-month follow-up, when they were 4.5 to 6.5 years old) from the integrated intervention arm, which combined teacher training and group-based parenting education (95). In this arm, children had significantly higher scores in measures of language and socio-emotional development than the comparison group and the teacher-training-only group. At the 36-month follow-up, however (when the children were 6–8 years old), a complex battery of child assessments showed that there were no sustained treatment effects on child development outcomes. The authors speculate that the effects faded out because once the children graduated from the CBCCs they were then absorbed into a low-quality primary school system that could not provide an appropriate learning environment that built on what the children had learned at the CBCC.

The impacts of early stimulation often fade out; this, however, is not destiny. A follow-up to the Jamaica trial 20 years later found that although benefits were deemed globally small at age 7 (63), by the time the children from the stimulation group reached adulthood their earnings were 25% higher than those of the control group (60). Similar long-term impacts of nutrition supplementation have been documented (70). Despite the longer-term effects on earnings found in the Jamaica trial, measures of IQ at age 18 showed that although the treatment improved relative to the stunted group without the intervention, they never reached the levels of the nonstunted group (133). The diversity of results, then, reinforces the need to trace the timeline of the results and to understand how different investments interact. In some cases, interventions that appear to fade out may actually be a temporary masking of impacts—an eclipse, as it were—rather than a full attenuation of impacts. Unfortunately, too few studies have followed individuals who participated in early childhood stimulation programs into their adult years to generalize any such eclipse.

Tracking recent program successes can serve as the first step to populate the literature on timelines. For example, the initial impacts of responsive stimulation and enhanced nutrition at age 2 in Pakistan were documented to persist two years after the program (138). Similarly, the results from scaled-up group-parenting support integrated with the CCT program in Mexico showed effects four years after the intervention was begun (51). Moreover, improved cognitive measures were noted for two CCT programs in Nicaragua. In one program, there was no fade-out two years after the emergency program ended (83), and the treatment group in the other program saw improvements in cognitive development but not physical outcomes seven years after the program ended (19).

#### 5. DIFFERENT ECONOMIC IMPLICATIONS FOR PRIORITIES IN NUTRITION AND EARLY CHILDHOOD DEVELOPMENT

#### 5.1. Implications of Current Evidence for Investments in Nutrition

What does the available evidence indicate about the economic returns on including stimulation with nutrition programs? The evidence for the returns on nutrition investments per se overlaps the evidence for stimulation in that the former is often dominated by productivity gains mediated through cognitive and socio-emotional skills. Thus, analytically, the measurement of economic benefits from productivity gains attributed to better nutrition is similar to the assessment of many of the gains from cognitive stimulation. Numerous studies indicate that these productivity gains mediated by nutrition through skill acquisition are extensive (8, 69, 71). Similarly, an extensive literature exists on the absolute and relative impact of different dimensions of cognitive and socio-emotions skills on earnings.

To elaborate, better nutrition is regularly associated with higher wages owing to nutrition's effect on schooling and to increased wages after controlling for schooling attainment (12). This association is noted even in high-income settings (35). However, given that stature and cognitive and socio-emotional development are jointly determined by a set of common factors, it is a challenge to separate the impact of height from other pathways. A few recent studies have investigated whether the association between height and wages is a proxy mainly for other measures of skills and capacity. In general, these studies confirm that the apparent association between stature and wages is attenuated when other skills are also included, but also that the impact of stature remains significant.

For example, Vogl (132) noted that height affected wages in Mexico through the selection process, whereby adults with greater stature sort into occupations that require greater cognitive rather than physical skills. This was also noted by LaFave & Thomas (76) in a study of Indonesia. Both studies controlled for cognitive and noncognitive skills. In Indonesia, a 1% increase in height was related to a 1.9% increase in hourly earnings when controlling for education and cognition (as measured by Raven's matrices as well as assessment of fluid intelligence and working memory, which are also significant explanatory variables). This increase was roughly half of the apparent relationship of wages and height when education and cognitive skills were excluded. Bossavie et al. (32) reached a similar conclusion in their study of male workers in Pakistan that included both Raven's matrices as well as an index of socio-emotional skills.

#### 5.2. Implications of Current Evidence for Investments in Child Development

There is less information, however, about the costs of the investments that are advocated to ensure that children reach their full potential, particularly in regard to costs for programs at scale. Moreover, only a small part of the various studies of economic returns on such investments—presented either as the benefits of programs or as the costs of neglecting potential investments, i.e., inaction—address the gains from integrating nutrition and child stimulation.

One form of investment for which estimating the additional costs and benefits of integration is analytically relatively straightforward is the inclusion of iron supplementation in daycare programs. As with similar studies in primary and secondary schools, the incremental costs of such programs are low and the benefits such as increased hemoglobin (Hb) and increased attendance are easy to document (31). However, to compare such improvements to the costs of the program, it is necessary to infer the monetary value of a change in Hb. For a study on daycare this generally involves inference using data from previous studies of adult populations. Lopez Boo et al. (80) conducted such an analysis, looking at the distribution of micronutrient packets to families of children in daycare in Nicaragua. The benefit-to-cost ratio is estimated to be above 1 under a range of assumptions and sensitivity analysis (implying the gains, discounted for the timing of future benefits, exceed the costs, including salaries).

Richter et al. (109) simulate the costs of adding UNICEF's Care for Development approach and WHO's package Thinking Healthy to existing health and nutrition programs. The model estimates that such services would cost an additional \$0.20 per capita in low-income countries and \$0.70 in upper-middle-income countries. Although this simulation is based on country-specific cost data, it cautions that given the assumptions needed to extrapolate globally the estimates are indicative; ex post studies would help validate the model.

There is a methodological dilemma in assessing the economic priorities of programs with multiple objectives. Ideally, all outcomes are placed in a common metric—usually the discounted sum of productivity gains over the lifetime of the beneficiaries plus an estimate of the value of reduced mortality. The number of assumptions required also makes it necessary to present a range of sensitivity analyses, which should strengthen the advocacy role but often does not. Alternatively, different programs and delivery mechanisms can be compared to determine which program is cost-effective for any given outcome. However, cost-effectiveness can be ambiguous when there are multiple outcomes.

A well-documented study of the relative costs of improving composite scores for language, as well as for cognitive development and motor development, in the successful integrated program in Pakistan acknowledges this limitation (61). Despite the details in this analysis, it is difficult to extrapolate given that the cost of integrated services was actually less than either service alone. While integration in a full-scale program may reduce the total cost compared to the sum of the individual components, it cannot be common that the combined service costs less than either element individually as was observed in the program in Pakistan.

Whether or not this particular study can be generalized, it points to a potential advantage of integrated programs. Even if there is no synergistic effect on outcomes, the cost to deliver two or more services that are bundled is often less than the sum of the costs of the individual components. This can be clearly indicated when the main costs of the program are tangible inputs, such as when vitamin A supplementation, deworming, and measles inoculations are jointly provided on child health days (52). Such economies of scope may be harder to achieve, however, when the programs involve extensive involvement of trained personnel and interaction with caregivers. The study by Gowani et al. (61) then stands out in regard to the questions it asks; in contrast, nutrition and stimulation dimensions of the full-scale program Hogares Comunitarios de Bienestar in Colombia as well as the integrated PIDI program in Bolivia were combined, so their components have not been costed out individually. The benefit-to-cost ratio of all components of the former program when assessed jointly was estimated to be between 1.0 and 2.7, discounting future benefits at 8% and 5%, respectively (22, 24). Assuming that the improvements in the latter program translated into more schooling at the intermediate level through grade 8, and based on returns to schooling in Bolivia, the benefit-to-cost ratio of the program ranged between 2 and 2.9 for discount rates of 5% and 3%, respectively.

However, despite favorable returns on investment the government of Bolivia canceled the program earlier than planned in the loan with the World Bank; it cost too much. Counting food (supplied initially by the World Food Program), it cost over \$450 per child per year in the late 1990s. At the time this exceeded 50% of the per capita GNP. This finding reflects the fact that sectoral investments are limited and the total costs of a program are as relevant as the expected benefits per dollar spent. Although data are not available to indicate what the benefit-to-cost ratio of the program would have been without the feeding component, or with a smaller snack substituting for the meals provided, less emphasis on food might have had a different yet still favorable prognosis. On the other hand, on the basis of school feeding experiences, the subsidy to meals may have been necessary for the most vulnerable—and potentially responsive—children to participate.

#### 5.3. Economic and Programmatic Implications of Potential Fade-Out of Program Effects

Parsing out nuances of the timeline of early childhood investments is essential to understand the economic value of such programs. Few economic analyses consider the variable costs that are needed over time to generate the expected benefits; even the welcomed increases of school enrollments and completion that are regularly attributed both to nutrition interventions and to early stimulation have an associated timeline of additional costs to educate these students. The timeline of the Head Start program in the United States illustrates this point. Although some evaluations found an apparent fade-out of initial impacts, particularly for African American beneficiaries, subsequent research argued that initial improvements would have resulted in gains from later investments in keeping with dynamic complementarities if beneficiaries from the preschool programs had received quality inputs following the initial program. As with the Malawi example discussed above, the apparent fade-out then points to a failure to provide the investments that theory and evidence would support; in this case, specifically, the authors speculate that the parenting support program was not sufficiently intensive to result in longer-term effects for children (41).

#### 5.4. Risk of Inequality and Inequity in Child Development

Missed opportunities for child development are costly not merely in terms of unrealized potential productivity but also in terms of equity. The legacy of missed opportunities even reaches across generations. This transmission may be based on the direct influence of maternal health on the growth of children (21). Moreover, the transmission may also continue through an indirect pathway; numerous studies indicate that the human capital implied by good maternal health leads to increased income, which subsequently influences investment in children. But additional pathways might reinforce the most obvious dynamics across generations; a recent analysis of the children of individuals in the Jamaica trial conducted in the 1980s found that children born to a stunted parent had lower development even after controlling for education, parental socioeconomic status, and the home environment (134).

This potential contribution to increased equity is hard to measure or place in a common metric with economic or other measures of benefits from enhanced development. However, as both poverty and low education are acknowledged risk factors, the question is how much value should be placed on this dimension when designing and prioritizing programs, not whether both nutrition and ECD programs inherently achieve intergenerational equity. Prioritization of such programs, however, depends not only on the social value of equity but also on the potential for offsetting early setbacks with subsequent investments. This refers back to the issues of self-productivity and dynamic substitutes and complements.

Grantham-McGregor et al. (62) identified seven efficacy studies that were targeted to children who were stunted, wasted, or anemic. These studies confirm that malnutrition is not an absolute barrier to potential benefits from enhanced stimulation. Indeed, the long-term evaluation of the Jamaica study found that the intervention increased earnings sufficiently for the treatment (stunted) group to catch up to the nonstunted comparison group. Similarly, the cognitive deficit between the first and fifth wealth quintiles of a sample of children in Bangladesh increased overall during the first 5 years of the lives of these children, but the gap was substantially mitigated by home stimulation (66). Moreover, in a study from Madagascar (47), up to 20% of the wealth gap in child development outcomes could be accounted for by household inputs, such as home stimulation, with the largest findings for receptive vocabulary and memory of phrases, which is a verbal measure of working memory (57). This longitudinal study, however, was observational and did not provide an intervention.

That such catch-up is possible is promising; whether or not stunting is irreversible, the fact that the associated cognitive consequences are demonstrably not fully irreversible implies a potential resilience. That is, those children who are stunted in their first 2 years of life—despite the best efforts of households, governments, and civil society—are not destined to be undereducated. This view does not challenge the overwhelming evidence that the earlier an investment can be made to prevent malnutrition or toxic stress, the higher the expected returns will be. Rather, the issue of catch-up addresses a social and rights-based need to design programs to ensure that the window for skills development is not shut prematurely on many children of low-income or marginalized families.

#### 5.5. Scaling Up Nutrition and Early Childhood Development Programs

Cost considerations may be a limiting factor when taking the evidence accumulated from small programs to a wider scale (109). Many of the most-well-studied programs have shown improvements among children who receive frequent home visits over several months. Although such interventions likely yield attractive benefit-to-cost ratios, especially over the longer term, this approach may be more manageable in terms of capacity constraints when the number of at-risk children is relatively small. More evidence of the effectiveness of other delivery models, using existing infrastructure and services, such as group sessions to provide opportunities to learn and practice responsive stimulating care, is urgently needed where possible. As community nutrition programs are an established platform for improving health (26), they provide a potential programmatic savings even in the absence of any impacts above those that are strictly additive. The Lady Health Worker trial (139) seems to fit this prospect.

Social protection systems may be another suitable delivery mechanism. They are already regularly used to incentivize nutrition by means of transfer programs including, but not limited to, CCTs (11, 111). For example, the ECD stimulation program in Colombia utilized the infrastructure of Familias en Acción, a CCT program designed to improve nutrition and schooling (16), as did Prospera (51). Both of these interventions built on the targeting mechanism for the program and established community liaisons. Similarly, Nicaragua used transfers to improve child development both with monitorable conditions (19) and, in a different program, with social marketing (83). In the case of Colombia, the additional services were costly, although as Attanasio (16) points out, not nearly as much as center-based programs. The costs in Mexico for the group-based care were also much lower because the parenting support sessions were group-based rather than home-based visits.

A key policy issue is whether the transfers would have been chosen in the absence of an ECD component. Most social protection programs are primarily designed for poverty alleviation and include human capital development as a means of adding development objectives to the existing goal of increased equity. Given that, in programs where there is little doubt that one component would be implemented whether or not the new service is included, only the additional costs exclusive of targeting or the delivery of cash benefits are appropriate for estimating benefit-to-cost ratios for ECD or nutrition programs linked to the social protection administration.

#### 5.6. Future Directions for Research

One direction for research implied by this review is to understand scaling up programs. In particular, cost data analysis is needed. Do joint programs reduce the total costs compared with two independent efforts, and if so, does it overload service provision and thus reduce one or more outcomes? Data on unit costs as coverage increases are also limited. For example, Horton et al. (72) assumed that the cost per beneficiary for increasing program delivery for nutrition-specific interventions beyond 80% of the population was twice as much as the average cost for reaching 80% of the population. Although this is plausible, there are little available data by which one can either verify or refute this or similar assumptions.

Moreover, relatively little evidence exists about whether the expected rates of return (or benefitto-cost ratios) will change as programs expand. Even the direction of change is uncertain. Reaching hard-to-cover populations may increase returns if benefits rise faster than the costs because of their relative deprivation; this may be an issue of the relationship between inputs and outputs at different starting conditions but it may also be an issue because there is social value from increasing equity. Alternatively, benefits may decline due to dilution of service quality as capacity constraints begin to bite. Capacity constraints are another dimension of costs; they may be partially offset with higher payments. Additionally, one needs to consider the costs, particularly time costs, for caregivers. Do the messages overload the resources of the household or can programs be designed to accommodate their time constraints?

Although self-productivity and dynamic complementarities have clear implications for prioritizing investments in early life, measuring either substitution or complementarities is difficult. The challenges of identifying contributions of nutritional and health inputs to cognitive and socio-emotional skills and of stimulation to nutrition are considerable. Most studies of returns on investments in health and skills development are not designed to assess whether these returns are higher or lower depending on past investments or current levels.

Still, strong evidence indicates that gaps in skills between children from low-resource families and those from families with more assets occur early in life (47, 114). In fact, a longitudinal study following children from age 3 into school age showed that socioeconomic gradients observed at preschool age persisted into school age across all developmental domains tested (57). Furthermore, an estimated 12–18% of the predicted wealth gap in school readiness at ages 7–10 can be accounted for by differences in home stimulation at the same age, even when controlling for early skills and initial endowments.

#### 6. CONCLUSIONS

In this review, we examined the nexus between nutrition and ECD by exploring evidence for benefits to growth and development associated with breastfeeding, complementary feeding, micronutrient and dietary supplementation, food fortification, and promotion of dietary diversity. We then presented evidence from longitudinal data in which we investigated plasticity and the timing of responses over stages in the life cycle and thus tried to understand critical periods for growth and development. Then, we examined a subset of programs that combined the delivery of nutrition services and child stimulation.

Our key observations revolve around the fact that children growing up in poverty in low- and middle-income countries are vulnerable because they do not receive the appropriate care, stimulation, or nutrition required to promote optimal child development. Nutritional deficiencies prior to conception and during pregnancy can result in neural tube disorders, low birth weight and length, and lifelong negative consequences, including developmental delays/disabilities, and substantial evidence supports the use of a wide range of interventions to prevent these deficiencies and conditions. Our review also highlights emerging evidence showing the potential for intergenerational effects of nutrition interventions that begin in early childhood and have lifelong consequences for the individual herself in addition to her offspring.

The promotion of nurturing care (e.g., access to good nutrition, responsive caregiving, quality health care, stable home environment) through the home environment can improve child development and nutrition outcomes and attenuate the negative effects of poverty. Whereas there is growing evidence that programs can improve cognitive and socio-emotional development after age 2, there is little evidence or experience demonstrating effects of interventions on linear growth after a child's second birthday, with the possible exception of a brief period of opportunity during puberty. Thus, early investment is crucial for the promotion of optimal nutritional and developmental outcomes, but with a smaller window of opportunity for linear growth than for other dimensions of development.

Numerous examples of programs show promising initial results that dissipate over time. Understanding the timeline of early childhood investments is essential to understanding the economic values of such programs over time. Economic models of adult capacities (physical, cognitive, socioemotional, executive function) view these as outcomes of investments in the life course, and this approach incorporates the possibility of early inputs fading out in subsequent periods or, alternatively, amplifying over time. Thus, complementary inputs are necessary to take full advantage of investments early in a child's life. This finding supports the logic of designing comprehensive programs over the life course that have no substantial gaps in the critical periods for both nutrition and cognitive development (108).

There is an active push for the promotion of integrated programs and packages (27–29), which is current despite the lack of evidence supporting benefits of integrated programs above and beyond the individual program components. This support for integration stems from the perceived benefits of coordinating with the health and nutrition sectors, for example, which are often the only services reaching children under 3 years of age. The urgent call for investment is supported by evidence that missed opportunities for promoting child development are costly not only in terms of unrealized potential productivity but also in terms of equity.

#### SUMMARY POINTS

- 1. Whereas there is growing evidence that programs can improve cognitive and socioemotional development after age 2, there is little evidence or experience demonstrating the effects of interventions on linear growth after a child's second birthday.
- 2. Nutritional deficiencies prior to conception and during pregnancy can result in neural tube disorders, low birth weight and length, and lifelong developmental delays/ disabilities.
- Emerging evidence shows the intergenerational effects of nutrition interventions that begin in early childhood have lifelong consequences for the individual herself in addition to her offspring.
- 4. Economic models of adult capacities (physical, cognitive, socio-emotional, executive function) view these as outcomes of investments in the life course; this approach incorporates the possibility of early inputs fading out in subsequent periods or, alternatively, amplifying over time depending on later investments.
- 5. There is a current push for the promotion of integrated programs and packages despite the lack of evidence supporting benefits of integrated programs above and beyond the individual program components. This support for integration stems from the perceived benefits of coordinating with the health and nutrition sectors, for example, which are often the only services reaching children under 3 years of age.
- 6. There are numerous examples of programs that show promising initial results that dissipate over time. Understanding the timeline of early childhood investments as well as subsequent ones is essential to understanding the economic values of such programs over time.
- 7. Missed opportunities for child development are costly not only in terms of unrealized potential productivity but also in terms of equity.

#### **FUTURE ISSUES**

- 1. There is a pressing need to understand how to scale up existing programs with proven efficacy so that the interventions can reach a broader population of vulnerable children and improve child nutrition and developmental outcomes.
- 2. A step toward reaching this goal would be to collect data on how both costs and benefits change as programs scale up.
- 3. There is also a need to examine cost-benefit analyses with an aim to understand whether integrated programs rather than independent efforts actually reduce total costs.
- 4. Researchers should also explore in greater detail what the independent, additive, and potentially synergistic effects of integrated programs can be in light of possible overload to service providers and beneficiaries.
- 5. Effective policy implementation requires the identification of the optimal government sectors that can be responsible for the promotion of ECD and nutrition benefits, especially the transition between core nutrition interventions and preschool years.
- 6. One objective is to increase the understanding of the consequences of poor maternal mental health and exposure to toxic stress during the prenatal period and in early childhood, and then to develop interventions to address these issues.
- 7. Social protection programs should experiment with the inclusion of parenting, nutritional, and early childhood support within the context of their services (e.g., microfinance and CCT programs).

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### LITERATURE CITED

- 1. Aboud FE, Akhter S. 2011. A cluster-randomized evaluation of a responsive stimulation and feeding intervention in Bangladesh. *Pediatrics* 127:e1191–97
- 2. Aboud FE, Singla DR, Nahil MI, Borisova I. 2013. Effectiveness of a parenting program in Bangladesh to address early childhood health, growth and development. *Soc. Sci. Med.* 97:250–58
- Aboud FE, Yousafzai AK. 2015. Global health and development in early childhood. Annu. Rev. Psychol. 66:433–57
- 4. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. 2007. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *Am. J. Clin. Nutr.* 86:412–20
- 5. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Zeilani M, et al. 2015. Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. *Am. J. Clin. Nutr.* 101:835–46

- Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Zeilani M, et al. 2017. Impact of small-quantity lipid-based nutrient supplement on hemoglobin, iron status and biomarkers of inflammation in pregnant Ghanaian women. *Matern. Child Nutr.* 13:e12262
- 7. Alderman H, Behrman JR, Grantham-McGregor S, Lopez-Boo F, Urzua S. 2014. Economic perspectives on integrating early child stimulation with nutritional interventions. *Ann. N. Y. Acad. Sci.* 1308:129–38
- Alderman H, Behrman JR, Puett C. 2017. Big numbers about small children: estimating the economic benefits of addressing undernutrition. *World Bank Res. Obs.* 32(1):107–25
- Alderman H, Glewwe P, Behrman J, Fernald LCH, Walker S. 2017. Evidence of impact on growth and development of interventions during early and middle childhood. In *Disease Control Priorities*, Vol. 8: *Child and Adolescent Health and Development*, ed. NDSD Bundy, SE Horton, D Jamison, G Patton. Washington, DC: World Bank. In press. 3rd ed.
- Alderman H, Hawkesworth S, Lundberg M, Tasneem A, Mark H, Moore SE. 2014. Supplemental feeding during pregnancy compared with maternal supplementation during lactation does not affect schooling and cognitive development through late adolescence. Am. J. Clin. Nutr. 99:122–29
- Alderman HH. 2016. Leveraging social protection programs for improved nutrition: summary of evidence prepared for the Global Forum on Nutrition-Sensitive Social Protection Programs, 2015. Work. Pap. 106265, World Bank, Washington, DC
- 12. Alderman HH, Sahn D. 2015. Public and private returns to investing in nutrition. In Oxford Handbook of Economics and Human Biology, ed. J Komlos, IR Kelly, pp. 405–22. New York: Oxford Univ. Press
- Alderman HH, Vegas E. 2011. The convergence of equity and efficiency in ECD programs. In No Small Matter: The Interaction of Poverty, Shocks, and Human Capital Investments in Early Childhood Development, ed. HH Alderman, pp. 155–83. Washington, DC: World Bank
- Andersen CT, Reynolds SA, Behrman JR, Crookston BT, Dearden KA, et al. 2015. Participation in the Juntos conditional cash transfer program in Peru is associated with changes in child anthropometric status but not language development or school achievement. *J. Nutr.* 145:2396–405
- Arimond M, Zeilani M, Jungjohann S, Brown KH, Ashorn P, et al. 2015. Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: experience from the International Lipid-Based Nutrient Supplements (iLiNS) Project. *Matern. Child Nutr.* 11(Suppl. 4):31–61
- Attanasio OP. 2014. Evidence on public policy: methodological issues, political issues and examples. Scand. J. Public Health 42:28–40
- Attanasio OP, Fernandez C, Fitzsimons EO, Grantham-McGregor SM, Meghir C, Rubio-Codina M. 2014. 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* 349:g5785
- Balogun OO, Dagvadorj A, Anigo KM, Ota E, Sasaki S. 2015. Factors influencing breastfeeding exclusivity during the first 6 months of life in developing countries: a quantitative and qualitative systematic review. *Matern. Child Nutr.* 11:433–51
- 19. Barham T, Macours K, Maluccio JA. 2013. Boys' cognitive skill formation and physical growth: long-term experimental evidence on critical ages for early childhood interventions. *Am. Econ. Rev.* 103(5):467–71
- Bassani DG, Arora P, Wazny K, Gaffey MF, Lenters L, Bhutta ZA. 2013. Financial incentives and coverage of child health interventions: a systematic review and meta-analysis. *BMC Public Health* 13(Suppl. 3):S30
- Behrman JR, Calderon MC, Preston SH, Hoddinott J, Martorell R, Stein AD. 2009. Nutritional supplementation in girls influences the growth of their children: prospective study in Guatemala. Am. J. Clin. Nutr. 90:1372–79
- 22. Behrman JR, Cheng Y, Todd PE. 2004. Evaluating preschool programs when length of exposure to the program varies: a nonparametric approach. *Rev. Econ. Stat.* 86:108–32
- Bendabenda J, Alho L, Ashorn U, Cheung YB, Dewey KG, et al. 2016. The effect of providing lipidbased nutrient supplements on morbidity in rural Malawian infants and young children: a randomized controlled trial. *Public Health Nutr.* 19:1893–903
- 24. Bernal R, Fernández C. 2013. Subsidized childcare and child development in Colombia: effects of Hogares Comunitarios de Bienestar as a function of timing and length of exposure. Soc. Sci. Med. 97:241–49
- 25. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, et al. 2014. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet* 384:347–70

- 26. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N. 2013. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? *Lancet* 382:452–77
- 27. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, et al. 2017. Early childhood development coming of age: science through the life course. *Lancet* 389(10064):77–90
- Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, et al. 2008. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 371:243–60
- 29. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, et al. 2013. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 382:427–51
- Blair C, Raver CC, Granger D, Mills-Koonce R, Hibel L. 2011. Allostasis and allostatic load in the context of poverty in early childhood. *Dev. Psychopathol.* 23:845–57
- Bobonis GJ, Miguel E, Puri-Sharma C. 2006. Anemia and school participation. J. Hum. Resour. XLI:692– 721
- 32. Bossavie I, Alderman HH, Giles J, Mete C. 2015. *The effect of height on earnings: Is stature just a proxy for cognitive and non-cognitive skills?* Presented at the Population Association of America 2015 Annual Meeting, Apr 30–May 2, San Diego, CA
- Britto PR, Lye SJ, Proulx K, Yousafzai AK, Matthews SG, et al. 2017. Nurturing care: promoting early childhood development. *Lancet* 389(10064):91–102
- 34. Casale D, Desmond C. 2016. Recovery from stunting and cognitive outcomes in young children: evidence from the South African Birth to Twenty Cohort Study. *J. Dev. Orig. Health Dis.* 7:163–71
- Case A, Paxson C. 2008. Stature and status: height, ability, and labor market outcomes. J. Polit. Econ. 116:499–532
- 36. Chang SM, Grantham-McGregor SM, Powell CA, Vera-Hernandez M, Lopez-Boo F, et al. 2015. Integrating a parenting intervention with routine primary health care: a cluster randomized trial. *Pediatrics* 136:272–80
- Christian P, Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, et al. 2010. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. *JAMA* 304(24):2716–23
- Crookston BT, Dearden KA, Alder SC, Porucznik CA, Stanford JB, et al. 2011. Impact of early and concurrent stunting on cognition. *Matern. Child Nutr.* 7:397–409
- Crookston BT, Schott W, Cueto S, Dearden KA, Engle P, et al. 2013. Postinfancy growth, schooling, and cognitive achievement: Young Lives. Am. J. Clin. Nutr. 98:1555–63
- 40. Cunha F, Heckman J. 2007. The technology of skill formation. Am. Econ. Rev. 97:31-47
- 41. Currie J, Thomas D. 1995. Does Head Start make a difference? Am. Econ. Rev. 85:341-64
- 42. Daelmans B, Black MM, Lombardi J, Lucas J, Richter L, et al. 2015. Effective interventions and strategies for improving early child development. *BMJ* 351:h4029
- De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. 2011. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database Syst. Rev.* (12):CD009085
- Desai A, Smith LE, Mbuya MN, Chigumira A, Fundira D, et al. 2015. The SHINE Trial Infant Feeding Intervention: pilot study of effects on maternal learning and infant diet quality in rural Zimbabwe. *Clin. Infect. Dis.* 61(Suppl. 7):S710–15
- 45. Dewey KG, Adu-Afarwuah S. 2008. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Matern. Child Nutr.* 4:24–85
- 46. Evans GW, Li D, Whipple SS. 2013. Cumulative risk and child development. Psychol. Bull. 139:1342-96
- 47. Fernald LC, Weber A, Galasso E, Ratsifandrihamanana L. 2011. Socioeconomic gradients and child development in a very low income population: evidence from Madagascar. *Dev. Sci.* 14:832–47
- Fernald LCH, Gertler PJ, Neufeld LM. 2008. Role of cash in conditional cash transfer programmes for child health, growth, and development: an analysis of Mexico's Oportunidades. *Lancet* 371:828–37
- Fernald LCH, Gertler PJ, Neufeld LM. 2009. 10-year effect of Oportunidades, Mexico's conditional cash transfer programme, on child growth, cognition, language, and behaviour: a longitudinal follow-up study. *Lancet* 374:1997–2005

- Fernald LCH, Hidrobo M. 2011. Effect of Ecuador's cash transfer program (Bono de Desarrollo Humano) on child development in infants and toddlers: a randomized effectiveness trial. Soc. Sci. Med. 72:1437–46
- Fernald LCH, Kagawa RMC, Knauer HA, Garcia Guerra A, Schnaas L, Neufeld LM. 2017. Promoting child development through group-based parent support within a cash transfer program: experimental effects on children's outcomes. *Dev. Psychol.* 53:222–36
- 52. Fiedler JL, Mubanga F, Siamusantu W, Musonda M, Kabwe KF, Zulu C. 2014. Child Health Week in Zambia: costs, efficiency, coverage and a reassessment of need. *Health Policy Plan.* 29:12–29
- Field E, Robles O, Torero M. 2009. Iodine deficiency and schooling attainment in Tanzania. Am. Econ. J.: Appl. Econ. 1:140–69
- 54. Fink G, Rockers PC. 2014. Childhood growth, schooling, and cognitive development: further evidence from the Young Lives study. *Am. J. Clin. Nutr.* 100:182–88
- 55. Fitzsimons E, Malde B, Mesnard A, Vera-Hernandez M. 2012. Household responses to information on child nutrition: experimental evidence from Malawi. IFS Work. Pap. W12/07, Institute for Fiscal Studies, London
- 56. Frongillo EA, Nguyen PH, Saha KK, Sanghvi T, Afsana K, et al. 2017. Large-scale behavior-change initiative for infant and young child feeding advanced language and motor development in a clusterrandomized program evaluation in Bangladesh. *J. Nutr.* 147:256–63
- 57. Galasso E, Weber A, Fernald LCH. 2017. Dynamics of child development: analysis of a longitudinal cohort in a very low income country. Policy Research Work. Pap. 7973, World Bank Econ. Rev., Washington, DC
- 58. Georgiadis A. 2017. The sooner the better but it's never too late: the impact of nutrition at different periods of childhood on cognitive development. Work. Pap. 159, Young Lives, London.
- Georgieff MK. 2007. Nutrition and the developing brain: nutrient priorities and measurement. Am. J. Clin. Nutr. 85:614s–20s
- Gertler P, Heckman J, Pinto R, Zanolini A, Vermeersch C, et al. 2014. Labor market returns to an early childhood stimulation intervention in Jamaica. *Science* 344:998–1001
- Gowani S, Yousafzai AK, Armstrong R, Bhutta ZA. 2014. Cost effectiveness of responsive stimulation and nutrition interventions on early child development outcomes in Pakistan. *Ann. N. Y. Acad. Sci.* 1308:149–61
- Grantham-McGregor SM, Fernald LC, Kagawa RM, Walker S. 2014. Effects of integrated child development and nutrition interventions on child development and nutritional status. *Ann. N. Y. Acad. Sci.* 1308:11–32
- Grantham-McGregor SM, Walker SP, Chang SM, Powell CA. 1997. Effects of early childhood supplementation with and without stimulation on later development in stunted Jamaican children. Am. J. Clin. Nutr. 66:247–53
- 64. Guldan G, Fan H, Ma X, Ni Z, Xiang X, Tang M. 2000. Culturally appropriate nutrition education improves infant feeding and growth in rural Sichuan, China. *7. Nutr.* 130:1204–11
- 65. Hamadani JD, Nahar B, Huda SN, Tofail F. 2014. Integrating early child development programs into health and nutrition services in Bangladesh: benefits and challenges. *Ann. N. Y. Acad. Sci.* 1308:192–203
- 66. Hamadani JD, Tofail F, Huda SN, Alam DS, Ridout DA, et al. 2014. Cognitive deficit and poverty in the first 5 years of childhood in Bangladesh. *Pediatrics* 134:e1001–8
- 67. Haroon S, Das JK, Salam RA, Imdad A, Bhutta ZA. 2013. Breastfeeding promotion interventions and breastfeeding practices: a systematic review. *BMC Public Health* 13(Suppl. 3):S20
- 68. Hess SY, Abbeddou S, Jimenez EY, Some JW, Vosti SA, et al. 2015. Small-quantity lipid-based nutrient supplements, regardless of their zinc content, increase growth and reduce the prevalence of stunting and wasting in young Burkinabe children: a cluster-randomized trial. PLOS ONE 10:e0122242
- Hoddinott J, Alderman HH, Behrman JR, Haddad L, Horton S. 2013. The economic rationale for investing in stunting reduction. *Matern. Child Nutr.* 9:69–82
- Hoddinott J, Behrman JR, Maluccio JA, Melgar P, Quisumbing AR, et al. 2013. Adult consequences of growth failure in early childhood. *Am. J. Clin. Nutr.* 98:1170–78
- Horton S, Alderman H, Rivera Dommarco J. 2009. Hunger and malnutrition. In *Global Crises, Global Solutions: Costs and Benefits*, ed. B Lomborg, pp. 305–54. Cambridge, UK: Cambridge Univ. Press
- 72. Horton S, Shekar M, McDonald CM, Mahal A, Brooks JK. 2009. *Scaling Up Nutrition: What Will It Cost*? Washington, DC: World Bank

- Timdad A, Yakoob MY, Bhutta ZA. 2011. Impact of maternal education about complementary feeding and provision of complementary foods on child growth in developing countries. *BMC Public Health* 11(Suppl. 3):S25
- 74. Kautz T, Heckman JJ, Diris R, ter Weel B, Borghans L. 2014. Fostering and measuring skills: improving cognitive and non-cognitive skills to promote lifetime success. NBER Work. Pap. No. 20749
- Kersten-Alvarez LE, Hosman CMH, Riksen-Walraven JM, Van Doesum KTM, Hoefnagels C. 2011. Which preventive interventions effectively enhance depressed mothers' sensitivity? A meta-analysis. *Infant Mental Health 7*. 32:362–76
- 76. LaFave D, Thomas D. 2017. Height and cognition at work: labor market productivity in a low income setting. *Econ. Hum. Biol.* In press
- 77. Lavy V, Schlosser A, Shany A. 2016. Out of Africa: human capital consequences of in utero conditions. NBER Work. Pap. 2184
- Lengua LJ, Zalewski M, Fisher P, Moran L. 2013. Does HPA-axis dysregulation account for the effects of income on effortful control and adjustment in preschool children? *Infant Child Dev.* 22:439–58
- 79. Li C, Zeng L, Wang D, Yang W, Dang S, et al. 2015. Prenatal micronutrient supplementation is not associated with intellectual development of young school-aged children. *J. Nutr.* 145:1844–49
- 80. Lopez Boo F, Palloni G, Urzua S. 2014. Cost-benefit analysis of a micronutrient supplementation and early childhood stimulation program in Nicaragua. *Ann. N. Y. Acad. Sci.* 1308:139–48
- Luby J, Belden A, Botteron K, Marrus N, Harms MP, et al. 2013. The effects of poverty on childhood brain development: the mediating effect of caregiving and stressful life events. *JAMA Pediatr*. 167:1135– 42
- 82. Macours K, Schady N, Vakis R. 2008. Can conditional cash transfer programs compensate for delays in early childhood development? Work. Pap., World Bank, Washington, DC. http://siteresources. worldbank.org/EXTLACREGTOPPOVANA/Resources/MacoursSchadyVakis\_031208.pdf
- 83. Macours K, Schady N, Vakis R. 2012. Cash transfers, behavioral changes, and cognitive development in early childhood: evidence from a randomized experiment. *Am. Econ. J.: Appl. Econ.* 4:247–73
- Manley J, Gitter S, Slavchevska V. 2013. How effective are cash transfers at improving nutritional status? World Dev. 48:133–55
- Maselko J, Sikander S, Bhalotra S, Bangash O, Ganga N, et al. 2015. Effect of an early perinatal depression intervention on long-term child development outcomes: follow-up of the Thinking Healthy Programme randomised controlled trial. *Lancet Psychiatry* 2:609–17
- Monteiro PO, Victora CG. 2005. Rapid growth in infancy and childhood and obesity in later life—a systematic review. *Obes. Rev.* 6:143–54
- 87. Moran P, Ghate D, van der Merwe A. 2004. *What works in parenting support? A review of the international evidence*. Policy Research Bureau, Res. Rep. 574, Nottingham, UK
- Mridha MK, Matias SL, Chaparro CM, Paul RR, Hussain S, et al. 2016. Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh. Am. J. Clin. Nutr. 103:236–49
- Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, Cole PM, et al. 2012. Preschool micronutrient supplementation effects on intellectual and motor function in school-aged Nepalese children. *Arch. Pediatr. Adolesc. Med.* 166:404–10
- Nahar B, Hossain I, Hamadani JD, Ahmed T, Grantham-McGregor S, Persson LA. 2015. Effect of a food supplementation and psychosocial stimulation trial for severely malnourished children on the level of maternal depressive symptoms in Bangladesh. *Child Care Health Dev.* 41:483–93
- Nahar B, Hossain MI, Hamadani JD, Ahmed T, Huda SN, et al. 2012. Effects of a community-based approach of food and psychosocial stimulation on growth and development of severely malnourished children in Bangladesh: a randomised trial. *Eur. J. Clin. Nutr.* 66:701–9
- Neville H, Pakulak E, Stevens C. 2015. Family-based training to improve cognitive outcomes for children from lower socioeconomic status backgrounds: emerging themes and challenges. *Curr. Opin. Behav. Sci.* 4:166–70
- Nowak C, Heinrichs N. 2008. A comprehensive meta-analysis of triple P-positive parenting program using hierarchical linear modeling: effectiveness and moderating variables. *Clin. Child Fam. Psychol. Rev.* 11:114–44

- Ozer EJ, Fernald LC, Manley J, Gertler PJ. 2009. Effects of a conditional cash transfer program on children's behavior problems. *Pediatrics* 123:e630–37
- Ozler B, Fernald LC, Kariger PK, McConnell C, Neuman MJ, Pinheiro Fraga E. 2016. Combining preschool teacher training with parenting education: a cluster-randomized controlled trial. CEGA Work. Pap. 062, Center for Effective Action, Univ. Calif., Berkeley
- Pasricha S-R, Hayes E, Kalumba K, Biggs B-A. 2013. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. *Lancet Glob. Health* 1:e77–86
- Paxson C, Schady N. 2010. Does money matter? The effects of cash transfers on child development in rural Ecuador. *Econ. Dev. Cultur. Change* 59:187–229
- Penny ME, Creed-Kanashiro HM, Robert RC, Narro MR, Caulfield LE, Black RE. 2005. Effectiveness
  of an educational intervention delivered through the health services to improve nutrition in young
  children: a cluster-randomised controlled trial. *Lancet* 365:1863–72
- Phuka JC, Maleta K, Thakwalakwa C, Cheung YB, Briend A, et al. 2008. Complementary feeding with fortified spread and incidence of severe stunting in 6- to 18-month-old rural Malawians. *Arch. Pediatr. Adolesc. Med.* 162:619–26
- Phuka JC, Maleta K, Thakwalakwa C, Cheung YB, Briend A, et al. 2009. Postintervention growth of Malawian children who received 12-mo dietary complementation with a lipid-based nutrient supplement or maize-soy flour. Am. J. Clin. Nutr. 90:382–90
- 101. Prado EL, Abbeddou S, Yakes Jimenez E, Some JW, Dewey KG, et al. 2017. Effects of an intervention on infant growth and development: evidence for different mechanisms at work. *Matern. Child Nutr.* 13:e12314
- 102. Prado EL, Dewey KG. 2014. Nutrition and brain development in early life. Nutr. Rev. 72:267-84
- 103. Prado EL, Maleta K, Ashorn P, Ashorn U, Vosti SA, et al. 2016. Effects of maternal and child lipidbased nutrient supplements on infant development: a randomized trial in Malawi. Am. J. Clin. Nutr. 103:784–93
- Prentice AM, Ward KA, Goldberg GR, Jarjou LM, Moore SE, et al. 2013. Critical windows for nutritional interventions against stunting. *Am. J. Clin. Nutr.* 97:911–18
- 105. Prudhon C, Langendorf C, Roederer T, Doyon S, Mamaty AA, et al. 2017. Effect of ready-to-use foods for preventing child undernutrition in Niger: analysis of a prospective intervention study over 15 months of follow-up. *Matern. Child Nutr.* 13:e12236
- 106. Qiu A, Anh TT, Li Y, Chen H, Rifkin-Graboi A, et al. 2015. Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Transl. Psychiatry* 5:e508
- 107. Rahman A, Malik A, Sikander S, Roberts C, Creed F. 2008. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. *Lancet* 372:902–9
- 108. Rao N, Sun J, Wong JM, Weekes B, Ip PS, Young MS, et al. 2014. Early childhood development and cognitive development in developing countries. Department for International Development, London. https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3465
- Richter LM, Daelmans B, Lombardi J, Heymann J, Lopez Boo F, et al. 2017. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. *Lancet* 389(10064):103–18
- Rollins NC, Bhandari N, Hajeebhoy N, Horton S, Lutter CK, et al. 2016. Why invest, and what it will take to improve breastfeeding practices? *Lancet* 387:491–504
- 111. Ruel MT, Alderman H, Maternal and Child Nutrition Study Group. 2013. Nutrition-sensitive interventions and programmes: How can they help to accelerate progress in improving maternal and child nutrition? *Lancet* 382:536–51
- 112. Sachdev H, Gera T, Nestel P. 2005. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. *Public Health Nutr.* 8:117–32
- 113. Sayyad-Neerkorn J, Langendorf C, Roederer T, Doyon S, Mamaty AA, et al. 2015. Preventive effects of long-term supplementation with 2 nutritious food supplements in young children in Niger. *J. Nutr.* 145:2596–603

- 114. Schady N, Behrman J, Araujo MC, Azuero R, Bernal R, et al. 2015. Wealth gradients in early childhood cognitive development in five Latin American countries. *J. Hum. Resour.* 50:446–63
- 115. Schott WB, Crookston BT, Lundeen EA, Stein AD, Behrman JR. 2013. Periods of child growth up to age 8 years in Ethiopia, India, Peru and Vietnam: key distal household and community factors. Soc. Sci. Med. 97:278–87
- 116. Shonkoff JP, Garner AS, The Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, Section on Developmental and Behavioral Pediatrics. 2012. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* 129:e232–46
- 117. Singla DR, Kumbakumba E, Aboud FE. 2015. Effects of a parenting intervention to address maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster-randomised trial. *Lancet Glob. Healtb* 3:e458–69
- 118. Soe NN, Wen DJ, Poh JS, Li Y, Broekman BF, et al. 2016. Pre- and post-natal maternal depressive symptoms in relation with infant frontal function, connectivity, and behaviors. *PLOS ONE* 11:e0152991
- 119. Stein AD. 2014. Nutrition in early life and cognitive functioning. Am. J. Clin. Nutr. 99:1-2
- 120. Sudfeld CR, McCoy DC, Danaei G, Fink G, Ezzati M, et al. 2015. Linear growth and child development in low- and middle-income countries: a meta-analysis. *Pediatrics* 135:e1266–75
- Surkan PJ, Kennedy CE, Hurley KM, Black MM. 2011. Maternal depression and early childhood growth in developing countries: systematic review and meta-analysis. *Bull. World Health Organ.* 89:608–15
- 122. Sweet MA, Appelbaum MI. 2004. Is home visiting an effective strategy? A meta-analytic review of home visiting programs for families with young children. *Child Dev.* 75:1435–56
- 123. Teivaanmäki T, Bun Cheung Y, Pulakka A, Virkkala J, Maleta K, Ashorn P. 2017. Height gain after two-years-of-age is associated with better cognitive capacity, measured with Raven's coloured matrices at 15-years-of-age in Malawi. *Matern. Child Nutr.* 13:e12326
- 124. Thompson RA, Nelson CA. 2001. Developmental science and the media. Early brain development. *Am. Psychol.* 56:5–15
- 125. Tomlinson M, Rotheram-Borus MJ, Harwood J, le Roux IM, O'Connor M, Worthman C. 2015. Community health workers can improve child growth of antenatally-depressed, South African mothers: a cluster randomized controlled trial. *BMC Psychiatry* 15:1–9
- 126. Tomlinson M, Rotheram-Borus MJ, le Roux IM, Youssef M, Nelson SH, et al. 2016. Thirty-six-month outcomes of a generalist paraprofessional perinatal home visiting intervention in South Africa on maternal health and child health and development. *Prev. Sci.* 17(8):937–48
- 127. Tripathy P, Nair N, Barnett S, Mahapatra R, Borghi J, et al. 2010. Effect of a participatory intervention with women's groups on birth outcomes and maternal depression in Jharkhand and Orissa, India: a cluster-randomised controlled trial. *Lancet* 375:1182–92
- 128. Uauy R, Kain J, Mericq V, Rojas J, Corvalan C. 2008. Nutrition, child growth, and chronic disease prevention. *Ann. Med.* 40:11–20
- 129. Vazir S, Engle P, Balakrishna N, Griffiths PL, Johnson SL, et al. 2013. 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.* 9:99–117
- 130. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, et al. 2008. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* 371:340–57
- Victora CG, Bahl R, Barros AJD, França GVA, Horton S, et al. 2016. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 387:475–90
- 132. Vogl TS. 2014. Height, skills, and labor market outcomes in Mexico. J. Dev. Econ. 107:84-96
- 133. Walker SP, Chang SM, Powell CA, Grantham-McGregor SM. 2005. Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: prospective cohort study. *Lancet* 366:1804–07
- Walker SP, Chang SM, Wright A, Osmond C, Grantham-McGregor SM. 2015. Early childhood stunting is associated with lower developmental levels in the subsequent generation of children. *J. Nutr.* 145:823– 28
- Walker SP, Grantham-McGregor SM, Himes JH, Powell CA, Chang SM. 1996. Early childhood supplementation does not benefit the long-term growth of stunted children in Jamaica. J. Nutr. 126:3017–24

- 136. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, et al. 2011. Inequality in early childhood: risk and protective factors for early child development. *Lancet* 378:1325–38
- 137. WHO. 2014. Global nutrition targets 2025: Policy Brief Series. World Health Organization. http://apps.who.int/iris/bitstream/10665/149018/1/WHO\_NMH\_NHD\_14.2\_eng.pdf
- 138. Yousafzai AK, Obradovic J, Rasheed MA, Rizvi A, Portilla XA, et al. 2016. Effects of responsive stimulation and nutrition interventions on children's development and growth at age 4 years in a disadvantaged population in Pakistan: a longitudinal follow-up of a cluster-randomised factorial effectiveness trial. *Lancet Glob. Health* 4:e548–58
- 139. Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. 2014. 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* 384:1282–93
- 140. Zimmermann MB. 2012. The effects of iodine deficiency in pregnancy and infancy. *Paediatr. Perinat. Epidemiol.* 26(Suppl. 1):108–17

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## Errata

An online log of corrections to *Annual Review of Nutrition* articles may be found at http://www.annualreviews.org/errata/nutr