Promoting Early Child Development With Interventions in Health and Nutrition: A Systematic Review

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abstract

CONTEXT: Although effective health and nutrition interventions for reducing child mortality and morbidity exist, direct evidence of effects on cognitive, motor, and psychosocial development is lacking.

OBJECTIVE: To review existing evidence for health and nutrition interventions affecting direct measures of (and pathways to) early child development.

DATA SOURCES: Reviews and recent overviews of interventions across the continuum of care and component studies.

STUDY SELECTION: We selected systematic reviews detailing the effectiveness of health or nutrition interventions that have plausible links to child development and/or contain direct measures of cognitive, motor, and psychosocial development.

DATA EXTRACTION: A team of reviewers independently extracted data and assessed their quality.

RESULTS: Sixty systematic reviews contained the outcomes of interest. Various interventions reduced morbidity and improved child growth, but few had direct measures of child development. Of particular benefit were food and micronutrient supplementation for mothers to reduce the risk of small for gestational age and iodine deficiency, strategies to reduce iron deficiency anemia in infancy, and early neonatal care (appropriate resuscitation, delayed cord clamping, and Kangaroo Mother Care). Neuroprotective interventions for imminent preterm birth showed the largest effect sizes (antenatal corticosteroids for developmental delay: risk ratio 0.49, 95% confidence interval 0.24 to 1.00; magnesium sulfate for gross motor dysfunction: risk ratio 0.61, 95% confidence interval 0.44 to 0.85).

LIMITATIONS: Given the focus on high-quality studies captured in leading systematic reviews, only effects reported within studies included in systematic reviews were captured.

CONCLUSIONS: These findings should guide the prioritization and scale-up of interventions within critical periods of early infancy and childhood, and encourage research into their implementation at scale.

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Mr Vaivada designed the study protocol, coordinated data extraction, and drafted the initial manuscript; Ms Gaffey designed the study protocol and data analysis plan and critically reviewed and revised the manuscript; Dr Bhutta conceptualized and designed the study, obtained funding, oversaw the data abstraction and analysis, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Despite recent improvement, in children <5 years old, high rates of mortality and morbidity, poverty, and chronic undernutrition are pervasive in many low- and middle-income countries (LMIC). For children who survive infancy, many remain at a high risk for stunted growth and impaired development. In 2014, ~23.8% of children (159 million) <5 years old were stunted1 and at a high risk of impaired child development.[2] The *Lancet*'s 2016 Early Child Development Series[3] estimated that based on stunting and extreme poverty, 43% of children (249.4 million) <5 years old in LMIC were at risk for suboptimal development,[4] which effectively forfeits a quarter of the annual adult income because of lost cognitive potential and reduced productivity.[5] Recent predictive modeling that used the Human Development Index, nutrition status, and Early Child Development Index data (from the Multiple Indicator Cluster Survey and Demographic Health Survey) suggests that 36.8% of children (80.8 million) ages 3 to 4 years in LMIC do not reach fundamental cognitive or socioemotional development milestones.[6] Moving forward, achieving the Sustainable Development Goals of zero hunger (Goal 2), good health and well-being at all ages (Goal 3), and quality and equitable education (Goal 4) will require maximizing every opportunity to institute appropriate interventions at scale.

To assist in selecting and prioritizing key interventions, we developed a conceptual framework of risk factors and opportunities for interventions across the life course (Fig 1).[7–9] For this overview, we were focused on the biological risk factors for suboptimal development, which broadly include undernutrition, infectious disease, and toxin exposure,[10] many of which affect both child survival and development.[7] There is also

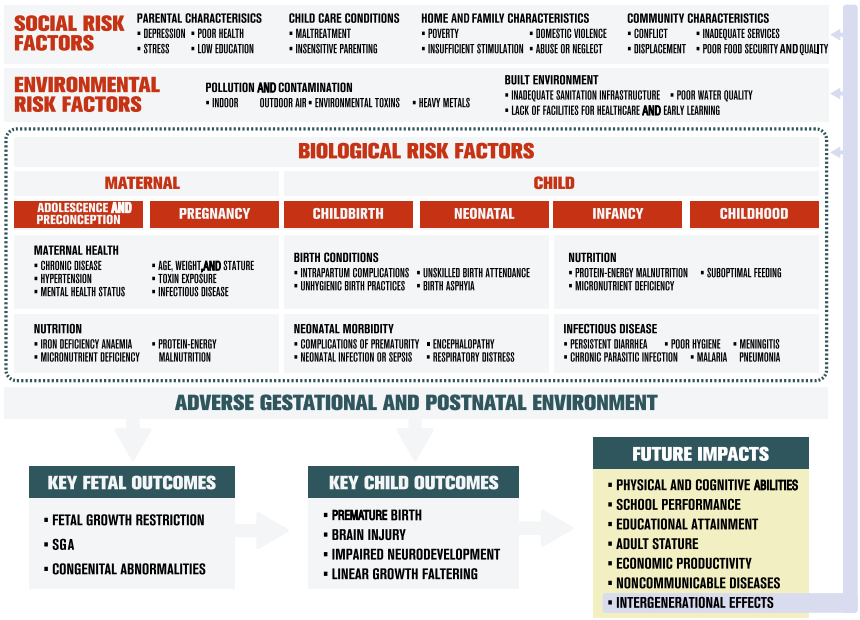

FIGURE 1

Conceptual framework of the risk factors in early life for suboptimal child growth and development. The dotted box highlights the focus of this overview on interventions that address biological risk factors.

evidence for an intergenerational impact of early stunting on child development[11] and a potential second window of opportunity for supporting development in the adolescent period.[12]

A variety of interventions that support maternal, newborn, and child health and nutrition (MNCH&N) have been identified as both effective and feasible for scale-up. The rationale for focusing on interventions that target the "First 1000 Days" of life (from conception to 2 years of age) is that the mitigation of risk factors during this critical period has substantial benefits over the life course.[13] There is evidence to suggest, however, that this period may be somewhat arbitrary because highly effective interventions also exist for the preconception period, late childhood, and adolescence that could benefit developmental outcomes. Nevertheless, supporting development in utero and early life is important and is when much of the fetal morbidity, stillbirths, and <5 years of age child mortality is concentrated.[3] With an increasing number of children surviving infancy, the importance of enhancing the survival agenda[7] to reduce morbidity and support child development is evident.

Table 1 summarizes the theoretical rationale for the beneficial neurodevelopmental impacts of a variety of interventions at various time points. Particularly impactful targets ameliorate maternal malnutrition and infection during preconception and pregnancy, which contribute to intrauterine growth restriction (IUGR), children being born small for gestational age (SGA), or preterm births, and neonatal infections. In addition to the developmental risks associated with maternal iodine deficiency[10] and folic acid deficiency,[14] recent evidence demonstrating the link between Zika virus infection during pregnancy and subsequent microcephaly in some infants[15] highlights the potential infectious risks to neurodevelopment in utero.[16] Postnatally, reducing environmental enteropathy is key because it may mediate the relationship between

poor personal and food hygiene and environmental factors that contribute to developmental deficits through chronic intestinal mucosal, systemic inflammation,[17] and nutrient malabsorption.[18] Both acute malnutrition and stunted growth in childhood are associated with poorer cognitive and motor development.[19] Despite these obvious links, most studies or programs of MNCH&N interventions typically only measure proximal measures, such as anthropometry, birth outcomes, or clinically apparent health outcomes. The associations between these intermediate outcomes and brain development are not only biologically plausible but have been demonstrated,[20] and they include IUGR,[21] preterm birth,[22] and neonatal insults[23] among others.

By building on recent overviews of evidence-based MNCH&N interventions,[36–40] we synthesized the outcome data on indirect risks and direct measures of early child development. We also mapped the outcome data to identify gaps in the evidence where additional research is needed.

METHODS

Identifying the Universe of Interventions to Assess

We identified (from recently published overviews) a universe of evidence-based interventions that have been identified in the literature as supporting MNCH&N and could plausibly affect early child development. The source overviews included relevant Lancet series[36–38] and summaries of essential intervention packages.[39,40] We restricted ourselves to interventions that target the biological risk factors for impaired child development and thus did not examine interventions related to education, poverty alleviation, the built environment, or other sectors that affect the social determinants of health.

TABLE 1 Theoretical Rationale for the Neurodevelopmental Impact of MNCH&N Interventions Through a Reduction in Risk Factors

Intervention Targets	Potential Mechanisms for Impact
Improving maternal physical, mental health, and nutritional status	Reduce inflammation and protect a developing fetus by preventing and treating infection.[9,16,23]
	Protect a fetus from maternal hormonal imbalances and deleterious epigenetic changes by reducing chronic stress[24] and preventing and treating depression.[25]
	Prevent IUGR and support optimal gestational growth and development by ensuring adequate food and micronutrient intake, particularly iodine and iron.[10]
Improving birth outcomes and reducing incidence of newborn complications, neonatal infection	Protect against neurologic damage by reducing the risk of preterm birth and complications associated with prematurity.[26]
	Ensure skilled birth attendance and hygienic delivery practices to prevent neurologic harm from sepsis.[23]
	Reduce complications and neurologic damage from birth asphyxia and associated hypoxia[23] by preventing obstructed labor, being large for gestational age, or postmature births and providing emergency cesarean deliveries and effective resuscitation when required.
Special care for preterm and SGA infants	Enhance lung adaptation and neuroprotection for vulnerable fetuses before imminent preterm birth with antenatal corticosteroids[27] and magnesium sulfate.[28]
	Provide appropriate thermal care and support prevention of neonatal infection, especially in preterm neonates who are vulnerable.[29,30]
	Delay cord clamping to maximize umbilical transfusion and improve iron stores.[31]
Promoting optimal infant and child nutrition, care, and growth	Promote optimal breastfeeding[9] and complementary feeding practices to protect against malnutrition, infection, enteropathy,[18] and linear growth stunting[10] and optimize gut microbiome development.[32]
	Ensure adequate psychosocial stimulation[10] is provided during the period of rapid brain development.
	Prevent and treat acute malnutrition and micronutrient deficiencies to prevent cognitive deficits.[10]
Infectious disease prevention and management in infancy and childhood	Provide routine childhood vaccinations and malaria prophylaxis,[10] which can prevent and mitigate direct neurologic damage from infectious agents.
	Support access to safe water, improve sanitation infrastructure, and promote hygienic practices to protect against environmental enteropathy and its sequelae.[18]
Reducing exposure to toxins and environmental contaminants	Minimize indoor air pollution to prevent placental pathology[33] and neurodevelopmental deficits.[34]
	Reduce lead and arsenic exposure[10] at home and in the workplace to protect against cognitive deficits.
	Support smoking cessation during pregnancy to prevent neurobehavioral deficits in children,[35] and address maternal drug and alcohol exposure.

Review Selection and Eligibility Screening

From the listing of interventions in each overview, citations for the corresponding systematic reviews and meta-analyses were extracted from the reference lists. We conducted relevant keyword searches in Medline, PubMed, and the Cochrane Database of Systematic Reviews for more recent reviews of pertinent interventions that were published in the past 2 years that may not have been captured in the overviews. Hand searching of relevant literature was also done to identify existing or forthcoming systematic reviews or meta-analyses for which data were available. Nonsystematic reviews, drug comparisons, reviews with no child-related outcome data, and those superseded by newer publications were excluded. Also excluded were reviews that focused on life-saving interventions to prevent maternal or perinatal mortality. If a cited Cochrane review had been updated, the most recent published version (up to April 1, 2016) was selected for data extraction.

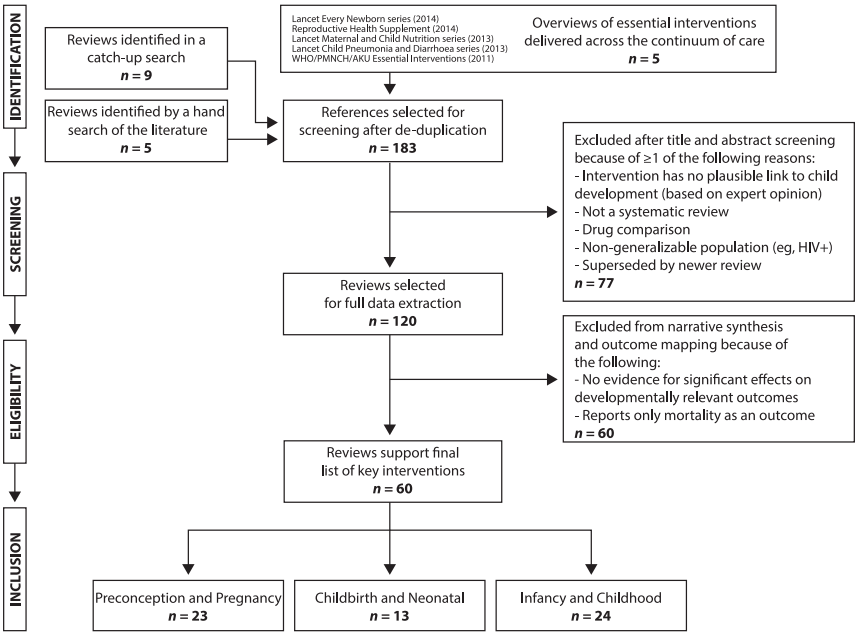

FIGURE 2
Overview flow diagram.

Data Extraction and Quality Assessment

Two reviewers used a standardized form to independently extract each review's characteristics, meta-analyzed the outcome data (including pooled effect sizes, confidence intervals, study counts, and heterogeneity), and performed A Measurement Tool to Assess Systematic Reviews (AMSTAR) quality assessments.[41] Any disagreements in the subjective quality ratings were resolved by consensus or a third reviewer. Additionally, we reviewed the focus, reported outcomes and characteristics of each study included within each review, retrieved the full text when relevant, and extracted any summary outcome data related to direct measures of child development.

Targeted Outcome Mapping

Interventions that included ≥1 statistically significant effect on an anthropometric, nutritional, severe morbidity or disability outcome or a direct measure of development (eg, Bayley Scales of Infant Development score or Ages and Stages Questionnaire score) were included in our final list of interventions with impact estimates. This encompassed direct effects on child development as well as effects on intermediate outcomes that are linked to development through a pathway related to malnutrition and infectious disease morbidity. Nonsignificant effect estimates for outcomes of interest for each included intervention are also displayed.

RESULTS

In total, 120 systematic reviews were selected for full data extraction, 60 of which were included in the outcome mapping exercise (see Fig 2). All but 1 of these received an AMSTAR rating of medium or high quality. Review characteristics, pooled effect estimates, and quality ratings are reported in Supplemental Table 7. Select interventions that had statistically significant effects on the outcomes of interest are highlighted below. The corresponding source overview for each highlighted intervention is summarized in Supplemental Figure 6.

Figure 3 displays a mapping of the outcomes reported in systematic reviews of the effectiveness of 35 selected interventions or intervention categories with promising effects on developmentally relevant outcomes. These are also depicted within a conceptual framework in Fig 4. Most commonly reported were birth outcomes for interventions delivered during preconception and pregnancy, growth outcomes and disease morbidity for interventions delivered during infancy and childhood, and mortality throughout these critical windows. Out of 60 reviews of interventions in which ≥1 statistically significant effect on an outcome of interest had been reported, only 16 reviews covering 13 discrete interventions reported summary estimates for outcomes that were direct measures of child development. Pooled data on direct measures of child development reported in meta-analyses often consisted of a small number of studies with relatively few participants when compared with other outcome types. Effect estimates for outcomes that directly measure child development and study characteristics of individual studies found within the reviews' meta-analyses are reported in Supplemental Table 8. Data for those individual studies with the direct measurements of child development included in reviews but not presented within their meta-analyses are found in Supplemental Table 9.

Preconception and Antenatal Care

Early preventive interventions that seek to minimize rates of SGA, prematurity, and newborn complications include supporting access to family planning and antenatal care services and an optimal environment for fetal growth (Table 2). Family planning for promoting

Critical Window	Interventions	Outcome Type				
		Improved Birth Outcomes, Growth, and Nutrition	Reduced Malformations, Disability and Injury	Reduced Severe Morbidity	Reduced Mortality	Improved Child Development
Preconception	Folic acid fortification and supplementation	Low birthweight	**Neural tube defects,** other defects		Stillbirth	
	Birth interval[b]	**SGA , Preterm birth**			**Infant**	
	Preconception diabetes care	Preterm birth, macrosomia	**Congenital malformation**		**Perinatal**	
Pregnancy	Antenatal corticosteroids (in appropriate populations)	SMG age	Cerebral palsy, visual/hearing impairment	**Intraventricular hemorrhage, respiratory distress syndrome , sepsis, necrotizing enterocolitis**	**Neonatal**	**Developmental delay[a]**
	Magnesium sulphate for women at risk of preterm birth		**Cerebral palsy,** blindness, deafness, major neurological disability	Intraventricular hemorrhage, apgar, convulsions	Fetal, neonatal	**Gross motor dysfunction,** neurodevelopmental delay, intellectual impairment, behavioural/learning difficulties
	Intermittent preventive therapy and insecticide-treated nets for malaria	**Low birth weight†, birth weight,** preterm birth	Congenital anomalies	Jaundice	**Perinatal[a] , infant, child ,** stillbirth	
	Antibiotics for premature rupture of membranes	**Birth weight,** low birth weight, preterm birth	**Cerebral abnormality,** serious disability at 7 years	**Neonatal infection,** necrotizing enterocolitis , respiratory distress syndrome	Perinatal	
	Antiplatelet agents	**Preterm birth, Small for gestational age**	Malformations at 18 months		**Fetal, neonatal**	**Poor motor function[a] ,** language comprehension/expression
	Lower genital tract infection screening and treatment	**Preterm birth, low birth weight**				
	Antibiotics for asymptomatic bacteriuria	**Low birth weight,** preterm birth				
	Detection and treatment of syphilis	**Preterm birth**		**Congenital syphilis**	**Stillbirth, neonatal**	
	Iodine supplementation	**Birthweight**	**Cretinism**		**Infant**	**Cognitive development**
	Iron and iron-folate supplementation	**Infant ferritin,** preterm birth, low birth weight				
	MMN supplementation	**SML age , low birth weight, preterm birth[a] , head circumference**	Congenital anomalies		**Stillbirth,** perinatal	Mental/psychomotor development
	Balanced protein-energy supplementation	**Low birth weight, Small for gestational age,** preterm birth, **birth length,** head circumference			**Stillbirth, neonatal**	Mental development
	Smoking cessation interventions	**Low birth weight, preterm birth**			Neonatal	
Labor and Birth	Continuous support during childbirth			**Apgar**		
	Delayed cord clamping	**Hematocrit, hemoglobin, iron deficiency**		**Intraventricular hemorrhage, necrotizing enterocolitis ,** respiratory distress syndrome , *jaundice*, **sepsis[a]**	**Neonatal[a] ,** infant	**Problem-solving/***personal-social* development, mental development
Neonatal	Therapeutic hypothermia for hypoxic ischemic encephalopathy		**Major developmental disability, MRI abnormalities, cerebral palsy,** blindness, deafness	**Seizures,** sepsis	**Neonatal, child**	**Neuromotor/developmental delay,** neuromotor/mental development
	Kangaroo mother care, skin-to-skin, plastic cap/wrap for thermal care	**Weight/length/head circumference gain, exclusive breastfeeding**	Cerebral palsy, deafness, visual impairment, major brain injury	**Sepsis, lower respiratory tract infection, severe illness, hypothermia , apgar**	**Neonatal[a] , infant**	**Mother-infant attachment,** psychomotor development
	Topical emollient therapy	**Weight/length/head circumference gain**		**Nosocomial infection,** invasive infection (low-income/ *high-income),* retinopathy of prematurity	**Neonatal**	
	Intramuscular vitamin K			**Hemorrhagic disease of the newborn**		
Infancy and Childhood	Rotavirus immunization			**Severe gastrointestinal infection**		
	Haemophilus influenzae B and pneumococcal immunization			**Severe pneumonia**	**Child[a]**	
	Handwashing behavior and water quality improvement	**Weight-for-age, Height-for-age**		**Diarrhea**	**Diarrhea[a]**	
	Vitamin A supplementation	**Vitamin A deficiency**	**Night blindness, xerophthalmia**	**Diarrhea, measles,** lower respiratory tract infection	**Child, diarrhea**	
	Iron supplementation	**Anemia, iron deficiency,** weight-for-age, height-for-age				**Motor[a] /mental development, intelligence quotient[a]**
	Multiple micronutrient provision	**Hemoglobin, anemia, iron deficiency**		*Diarrhea*		**Academic performance, motor milestone score,** fluid/crystallized intelligence
	Zinc supplementation and treatment for acute diarrhea	**Height gain, zinc deficiency,** *ferritin* , stunting		**Severe/persistent diarrhea,** *lower respiratory tract infection* , **Pneumonia,** malaria, hospitalization	Child, diarrhea, lower respiratory tract infection, **pneumonia,** malaria	Mental/psychomotor development
	Intermittent preventive therapy and bed nets for malaria	**Anemia[a] , hemoglobin**		**Severe malaria,** hospitalization	Child	
	Deworming drug treatment	**Weight, height, Mid-upper arm circumference, skin fold thickness,** hemoglobin			Child	
	Breastfeeding promotion, education, and support	**Exclusive breastfeeding, early initiation of breastfeeding**				
	Complementary feeding education and provision	**Stunting, height gain, weight gain, underweight**		**Respiratory infection**		
	Supplementary feeding	**Hemoglobin, weight-for-age, height-for-age**				**Psychomotor development, cognitive development†**
	Treatment for moderate and severe acute malnutrition	**Weight-for-age, weight -for-height, mid-upper arm circumference**		**Moderate acute malnutrition recovery**		

FIGURE 3

Mapping of the outcomes reported in reviews of the impact of interventions across the continuum of care. Bold text shows pooled outcome(s) reported with significant beneficial effect(s). Regular text shows pooled outcome(s) reported with nonsignificant effect(s). Italic text shows pooled outcome(s) reported with significant detrimental effect(s). [a] Pooled outcomes reported in 2 or more separate meta-analyses with both significant beneficial and nonsignificant and/or detrimental effects (eg, different subgroups). [b] Effects from observational data, rather than a family planning intervention.

longer birth intervals can improve birth outcomes,[42] and preconception diabetes care can reduce perinatal mortality and congenital malformations.[43] Antiplatelet agents can prevent preeclampsia in at-risk women, improve infant growth and birth outcomes, and prevent motor deficits in infancy.[27]

Infection and inflammation during pregnancy negatively influence fetal growth and development. Malaria prophylaxis;[44–46] antibiotic treatment of asymptomatic bacteriuria,[47] a confirmed infection,[48] or preterm membrane rupture[49]; and smoking cessation interventions[50] can all

improve pregnancy and birth outcomes. Magnesium sulfate given to mothers who are at risk for preterm birth reduce infants' risk of cerebral palsy and gross motor dysfunction.[28] In appropriate populations,[51] antenatal corticosteroids for women who are at risk for preterm birth prevent intracranial hemorrhage and developmental delay in childhood[52] as well as neonatal mortality in both high- and low-income settings.[53]

Nutrition During Preconception and Pregnancy to Optimize Fetal Growth and Development

Adequate macronutrient intake is essential for optimal fetal growth and development, and balanced protein-energy supplementation during pregnancy improves fetal growth and birth outcomes, with greater effects observed in malnourished women.[54] Provision of nutrient supplements to food-insecure or wasted expectant mothers supports optimal growth and development both in the womb and after birth (Table 3). The significant effects of the aforementioned interventions on key birth outcomes are summarized in Fig 5. Adequate micronutrient intake is essential for satisfying the physiologic requirements of a developing fetus. Ideally, interventions to address maternal undernutrition and micronutrient deficiencies should start in the preconception period.[55] Folic acid supplementation[56] and fortification[57] during preconception effectively prevents neural tube defects. During pregnancy, folic acid also improves birth weight,[43] and iodine supplementation in deficient populations prevents cretinism and infant mortality and improves cognitive development.[58] Observational studies reveal that the use of iodized salt in at-risk populations is a cost-effective way to improve iodine status and confers substantial benefits to

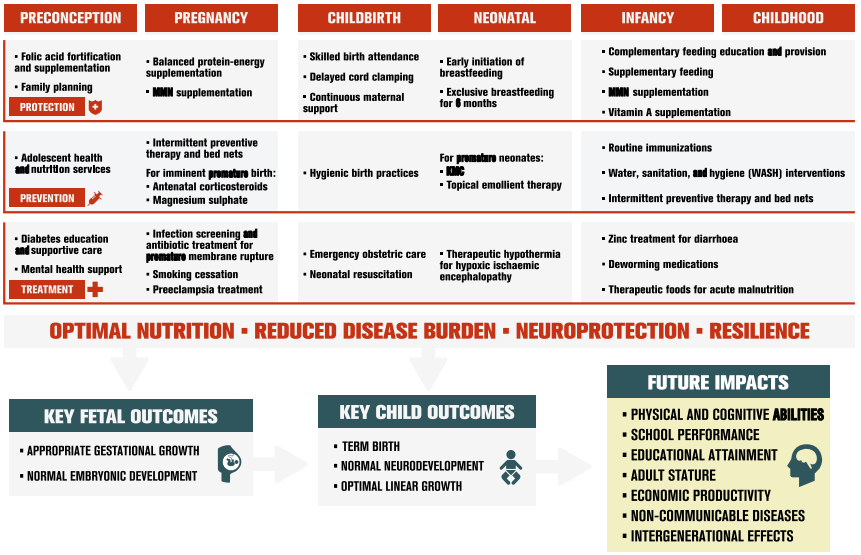

FIGURE 4
Conceptual framework of key interventions in early life that support optimal child growth and development.

cognition.[58] Iron supplementation during pregnancy[59] improves birth outcomes and infant iron status in areas with high malarial burden, with potential developmental benefits seen in areas with a high burden of iron deficiency (See Supplemental Table 9). A Cochrane review reveals that multiple micronutrient (MMN) supplementation during pregnancy[60] can reduce the prevalence of SGA, low birth weight, and preterm births, with potential cognitive and motor development benefits (see Supplemental Table 9) and gains in head circumference[61] in the offspring of undernourished mothers. Notwithstanding these potential benefits, a recent review[61] of MMN supplementation in pregnancy did not find any developmental benefits in the limited set of studies that had measured such outcomes.

Care During Labor, Birth, and the Neonatal Period to Prevent Complications and Morbidity

The provision of appropriate and skilled care during labor, birth, and the immediate newborn period should be afforded to all infants, with additional protective interventions for at-risk neonates (Table 4). Of newborns, ~3% to 6% require basic resuscitation at birth, and providing training in neonatal resuscitation impacts neonatal mortality.[62,63] Skilled birth attendance in community settings reduces perinatal and early neonatal mortality and risks of morbidity associated with intrapartum complications.[64] Social support for women during childbirth has been shown to improve Apgar scores in neonates, which underscores the importance of addressing maternal anxiety and stress.[63] Appropriate aftercare and strategies to protect the brains of newborns after birth asphyxia can further mitigate neurodevelopmental deficits and disabilities. Therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy reduces the risk of developmental delay and cerebral palsy, although evidence is currently lacking from LMIC.[65] Delayed cord clamping in preterm neonates reduce the risks for intraventricular hemorrhage[23,66] and anemia,[66] but the reported effects on neurodevelopment are mixed.[67] In addition to its survival benefits, Kangaroo Mother Care (KMC) in preterm infants has been shown to improve mother-infant attachment,

TABLE 2 Review of Key Impacts of Health Interventions Delivered During Preconception and Pregnancy

Key Interventions	Summary Effects With Implications for Developmental Outcomes (Direct Developmental Effects)
Preconception diabetes care, 1 SR, HIC and LMIC	Improved fetal development: reduced risk of congenital malformations (RR 0.30, 95% CI 0.22 to 0.41; *N* = 4760 in 20 studies)
Antiplatelet agents in pregnancy for preeclampsia prevention, 1 SR, HIC and LMIC	Improved birth outcomes: reduced risk of preterm birth (RR 0.92, 95% CI 0.88 to 0.97; *N* = 31 151 in 29 studies), SGA birth (RR 0.90, 95% CI 0.83 to 0.98; *N* = 23 638 in 36 studies) Fewer motor deficits in infancy: reduced risk of poor gross or fine motor function at 18 mo (RR 0.49, 95% CI 0.26 to 0.91; *N* = 788 in 1 study) Nonsignificant effects: poor gross motor function at 18 mo (RR 0.82, 95% CI 0.57 to 1.17; *N* = 4365 in 1 study), poor language expression at 18 mo (RR 0.94, 95% CI 0.74 to1.19; *N* = 4365 in 1 study)
IPTp and insecticide-treated bed nets for malaria prevention, 3 SRs, LMIC	Improved birth weight: IPTp with sulfadoxine-pyrimethamine reduced risk of low birth weight (RR 0.81, 95% CI 0.67 to 0.99; *N* = 3043 in 7 studies) and IPTp combined with bed net usage reduced risk of low birth weight (RR 0.65, 95% CI 0.55 to 0.77; *N* = 3360 in 5 studies)
Antibiotics for premature rupture of membranes, 2 SR, HIC and LMIC	Longer gestation: reduced the chance of birth within 7 d of treatment (RR 0.79, 95% CI 0.71 to 0.89; *N* = 5965 in 7 studies) Fewer brain injuries: reduced risk of major cerebral abnormalities on ultrasound (RR 0.81, 95% CI 0.68 to 0.98; *N* = 6289 in 11 studies) Protection from infection: reduced risk of neonatal infections including pneumonia (RR 0.67, 95% CI 0.52 to 0.85; *N* = 1680 in 12 studies)
Lower genital tract infection screening and treatment, 1 SR, HIC	Improved birth outcomes: reduced risk of preterm birth (RR 0.55, 95% CI 0.41 to 0.75; *N* = 4155 in 1 study) and preterm and low birth weight (RR 0.48, 95% CI 0.34 to 0.66; *N* = 4155 in 1 study)
Antibiotics for asymptomatic bacteriuria, 1 SR, HIC	Improved birth outcomes: reduced risk of preterm birth (RR 0.27, 95% CI 0.11 to 0.62; *N* = 242 in 2 studies) and low birth weight (RR 0.64, 95% CI 0.45 to 0.93; *N* = 1437 in 6 studies)
Detection and treatment of syphilis, 1 SR, HIC and LMIC	Improved birth outcomes: reduced risk of preterm birth (RR 0.36, 95% CI 0.27 to 0.47; *N* = 1959 in 7 studies) Protection from syphilis infection at birth: reduced risk of congenital syphilis (RR 0.03, 95% CI 0.02 to 0.07; *N* = 3460 in 3 studies)
Smoking cessation interventions, 1 SR, HIC and LMIC	Improved birth outcomes: reduced risk of low birth weight (RR 0.82, 95% CI 0.71 to 0.94; *N* = 8562 in 14 studies) and preterm birth (RR 0.82, 95% CI 0.70 to 0.96; *N* = 7852 in 14 studies)
Magnesium sulfate for neuroprotection in imminent preterm births, 1 SR, HIC and LMIC	Protection from motor disability and dysfunction: reduced risk of cerebral palsy (RR 0.68, 95% CI 0.54 to 0.87; *N* = 6145 in 5 studies) and gross motor dysfunction (RR 0.61, 95% CI 0.44 to 0.85; *N* = 5980 in 4 studies) Nonsignificant effects: developmental delay or intellectual impairment (RR 0.99, 95% CI 0.91 to 1.09; *N* = 5980 in 4 studies)
Antenatal corticosteroids, 2 SRs, HIC and LMIC	Fewer neonatal complications: reduced risk of cerebroventricular hemorrhage (RR 0.54, 95% CI 0.43 to 0.69; *N* = 2872 in 12 studies), respiratory distress syndrome (RR 0.66, 95% CI 0.59 to 0.73; *N* = 4038 in 21 studies), sepsis within 48 h (RR 0.56, 95% CI 0.38 to 0.85; *N* = 1319 in 4 studies), and necrotizing enterocolitis (RR 0.46, 95% CI 0.29 to 0.74; *N* = 1675 in 8 studies) Improved child development: reduced risk of developmental delay in childhood (RR 0.49, 95% CI 0.24 to 1.00; *N* = 518 in 2 studies) Nonsignificant effects: neurodevelopmental delay in childhood (RR 0.64, 95% CI 0.14 to 2.98; *N* = 988 in 1 study), intellectual impairment in childhood (RR 0.86, 95% CI 0.44 to 1.69; *N* = 778 in 3 studies), and behavioral and/or learning difficulties in childhood (RR 0.86, 95% CI 0.35 to 2.09; *N* = 90 in 1 study)

CI, confidence interval; HIC, high-income country; IPTp, intermittent preventive therapy in pregnancy; RR, risk ratio; SR, systematic review.

rates of exclusive breastfeeding, and growth rates[68] and prevent pneumonia, sepsis, jaundice,[69] and hypothermia.[70] Skin-to-skin contact, which is a core component of KMC, can improve measures of infant cardiorespiratory stability.[71] Topical emollient therapy for preterm infants, which is a neonatal skincare strategy for hypothermia and infection prevention, can improve infant growth[72] and prevent hospital-acquired infections and neonatal mortality.[73] Cleminson and McGuire[72] conducted a small study and showed improved psychomotor development in low-risk preterm neonates (see Supplemental Table 9). Massage therapy in preterm infants has been found to promote weight gain when coconut or sunflower oil is used.[74]

Nutrition During Infancy and Childhood for Optimal Growth and Development

A variety of effective nutritional interventions exist that are delivered during infancy and childhood, when rapid growth and development occur (Table 5). Breast milk regulates infant immunity, metabolic processes, and brain development, which are mediated through the establishment of the intestinal microbiome.[75] Optimal breastfeeding is linked to significant reductions in infectious disease mortality, diarrhea, and lower respiratory infections.[76–78] Breastfeeding can impact cognitive development during infancy, and whereas there is debate about the magnitude of effect,[79,80] meta-analysis of observational data[81] and a single randomized controlled trial[82] suggest improved intelligence. Various effective breastfeeding education or support interventions exist that increase the coverage of early and exclusive breastfeeding[83] with a consistently larger effect size in LMIC settings.[84] A recent Lancet

TABLE 3 Review of Key Impacts of Nutrition Interventions Delivered During Preconception and Pregnancy

Key Interventions	Summary Effects With Implications for Developmental Outcomes (Direct Developmental Effects)
Folic acid fortification and supplementation for women of childbearing age, 3 SRs, HIC and LMIC	Prevention of neural tube defects: reduced risk of neural tube defects with supplementation (RR 0.31, 95% CI 0.17 to 0.58; *N* = 6708 in 5 studies) and fortification (RR 0.59, 95% CI 0.52 to 0.68; 11 studies)
Iodine supplementation, 1 SR, HIC and LMIC	Protection from severe developmental deficits: reduced risk of cretinism (RR 0.27, 95% CI 0.12 to 0.60; *N* = 9500 in 5 studies) Improved cognitive development: 10% to 20% increase in cognitive development scores (*N* = 1200 in 4 studies)
Iron and iron-folate supplementation, 1 SR, HIC and LMIC	Improved birth outcomes: reduced risk of early-preterm (<34 wk) birth (RR 0.51, 95% CI 0.29 to 0.91; *N* = 3743 in 5 studies) and reduced risk of low birth weight (RR 0.83, 95% CI 0.73 to 0.94; *N* = 4645 in 5 studies) in areas with high malarial burden only Improved infant iron stores: increased infant (<6 mo) serum ferritin concentration (MD 11.00 μg/L, 95% CI 4.37 to 17.63; *N* = 197 in 1 study)
MMN supplementation, 2 SRs, HIC and LMIC	Improved birth outcomes: reduced risk of SGA birth (RR 0.91, 95% CI 0.84 to 0.97; *N* = 67 036 in 14 studies), low birth weight (RR 0.88, 95% CI 0.85 to 0.90; *N* = 70 044 in 15 studies), and preterm birth in underweight (BMI <20) mothers (RR 0.85, 95% CI 0.80 to 0.90; 4 studies) Improved growth during gestation: increased head circumference (SMD 0.08, 95% CI 0.00 to 0.15; *N* = 2692 in 4 studies) Nonsignificant effects: mental development scores at 6 mo (MD −0.02, 95% CI −6.78 to 6.74; *N* = 770 in 1 study) and 12 mo (MD 1.21, 95% CI −5.06 to 7.48; *N* = 744 in 1 study) and psychomotor development scores at 6 mo (MD −0.16, 95% CI −3.91 to 3.59; *N* = 770 in 1 study) and 12 mo (MD 0.34, 95% CI −2.73 to 3.41; *N* = 744 in 1 study)
Balanced protein-energy supplementation, 1 SR, HIC and LMIC	Improved birth outcomes: reduced risk of low birth weight (RR 0.68, 95% CI 0.51 to 0.92; *N* = 522 in 5 studies) and SGA birth (RR 0.66, 95% CI 0.49 to 0.89; *N* = 5250 in 9 studies) Augmented linear growth during gestation: increased birth length (MD 0.16 cm, 95% CI 0.02 to 0.31; *N* = 3698 in 7 studies) Nonsignificant effects: mental development scores at 1 y (MD −0.74, 95% CI −1.95 to 0.47; *N* = 411 in 1 study)

CI, confidence interval; HIC, high-income country; MD, mean difference; RR, risk ratio; SMD, standard mean difference; SR, systematic review.

series[85] outlined a variety of sectors in which breastfeeding promotion is effective at improving early and exclusive breastfeeding rates.[86]

Given the link between childhood anemia and cognition,[87] there is interest in addressing childhood deficiency in iron and other micronutrients. A Cochrane review[88] of intermittent iron supplementation in children 0 to 12 years old found improvements in motor development but a decrease in IQ. In another review, Sachdev, Gera, and Nestel[89] examined iron supplementation in children 0 to 15 years old and found improvements in mental development scores. MMN supplementation can improve motor development in infants 6 to 12 months old and academic performance in school-aged children.[90] Reductions in iron deficiency anemia have also been observed[91] in addition to better motor milestone attainment (see Supplemental Table 9). Vitamin A supplementation in children effectively reduces vitamin A deficiency and associated morbidities,[92] including reductions in all-cause and diarrhea-associated mortality.[92]

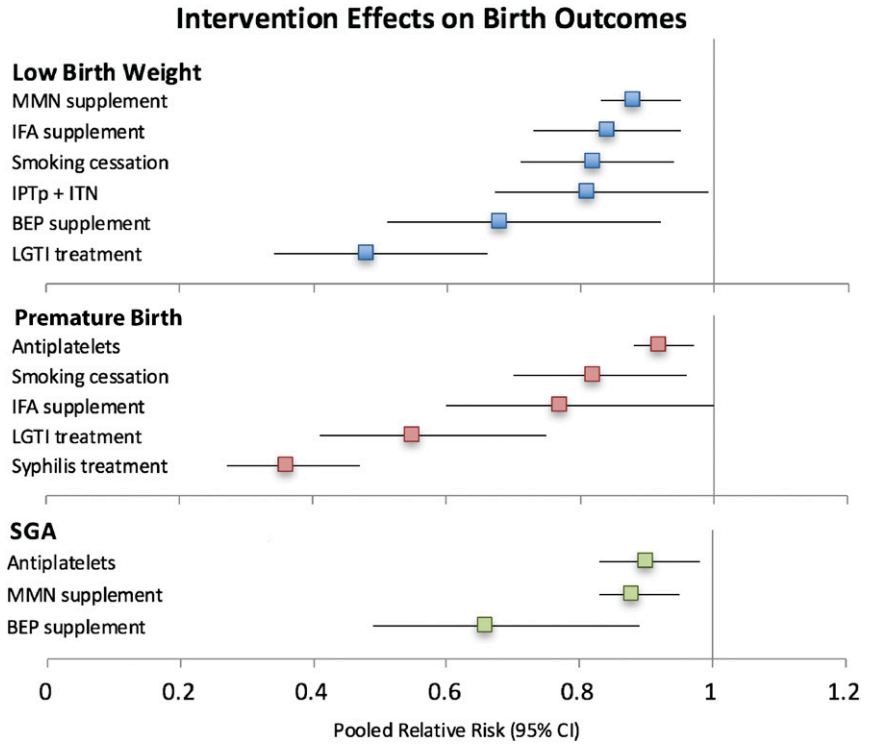

FIGURE 5
Range of effects of interventions during pregnancy on birth outcomes. BEP, balanced protein-energy; CI, confidence interval; IFA, iron-folic acid; IPTp, intermittent preventive therapy for malaria during pregnancy; ITN, insecticide treated nets; LGTI, lower genital tract infection.

Complementary feeding education for parents in food-secure populations improves infant growth and also decreases stunting in food-insecure populations.[93] Food provision in food-insecure populations can

TABLE 4 Review of Key Impacts of Interventions Delivered in the Neonatal Period

Key Interventions	Summary Effects With Implications for Developmental Outcomes (Direct Developmental Effects)
Delayed cord clamping, 4 SRs, HIC, and LMIC	Fewer complications of prematurity: reduced risk of intraventricular hemorrhage in preterm (RR 0.59, 95% CI 0.41 to 0.85; *N* = 539 in 10 studies) and early-preterm neonates (RR 0.62, 95% CI 0.43 to 0.91; *N* = 390 in 9 studies) and reduced risk of necrotizing enterocolitis (RR 0.62, 95% CI 0.43 to 0.90; *N* = 241 in 5 studies) Improved iron status: in premature infants, increased hematocrit at 24 h (MD 3.28, 95% CI 1.34 to 5.22; *N* = 199 in 3 studies); in extremely low birth weight infants, increased hemoglobin on NICU admission (MD 3.42 g/dL, 95% CI 3.11 to 3.74; *N* = 137 in 10 studies); and in term infants, reduced iron deficiency at 3–6 mo (early versus delayed RR 2.65, 95% CI 1.04 to 6.73; *N* = 1152 in 5 studies) Reduced risk of infection: decreased odds of late-onset sepsis in extremely low birth weight infants (OR 0.39, 95% CI 0.18 to 0.81; 10 studies) Mixed effects on development at 4 mo in term infants: improved problem-solving ASQ score (MD 1.80, 95% CI 0.22 to 3.38; *N* = 365 in 1 study) and reduced personal-social ASQ score (MD −2.30, 95% CI −4.09 to −0.51; *N* = 365 in 1 study) Nonsignificant effects: total ASQ score at 4 mo (MD −1.40, 95% CI −7.31 to 4.51; *N* = 365 in 1 study) and BSID mental development score <70 at 24 mo (OR 0.52, 95% CI 0.14 to 1.98; 2 studies)
Therapeutic hypothermia for hypoxic ischemic encephalopathy, 1 SR, HIC, and LMIC	Reduced cognitive developmental and motor disability: reduced risk of major developmental disability (RR 0.77, 95% CI 0.63 to 0.94; *N* = 1344 in 8 studies), cerebral palsy (RR 0.66, 95% CI 0.54 to 0.82; *N* = 881 in 7 studies), neuromotor delay (RR 0.75, 95% CI 0.59 to 0.94; *N* = 657 in 6 studies), and developmental delay (RR 0.74, 95% CI 0.58 to 0.94; *N* = 667 in 6 studies) Nonsignificant effects: neuromotor development score (MD 0.77, 95% CI −4.39 to 5.94; *N* = 271 in 3 studies) and mental development score (MD 2.47, 95% CI −2.77 to 7.71; *N* = 271 in 3 studies)
KMC, skin-to-skin contact, and other thermal care methods in preterm infants, 4 SR, HIC, and LMIC	Improved feeding practices: more exclusive breastfeeding at 1–3 mo (RR 1.20, 95% CI 1.01 to 1.43; *N* = 600 in 5 studies) and 3–6 mo (RR 1.97, 95% CI 1.37 to 2.83; *N* = 149 in 3 studies) Reduced risk of infection: reduced risk of sepsis (RR 0.56, 95% CI 0.40 to 0.78; *N* = 1343 in 7 studies) Improved mother-infant attachment score (MD 6.24, 95% CI 5.57 to 6.91; *N* = 100 in 1 study) Nonsignificant effects: psychomotor development at 12 mo (MD 1.05, 95% CI −0.75 to 2.85; *N* = 579 in 1 study)
Topical emollient therapy, 2 SR, HIC, and LMIC	Reduced infection risk in preterm infants: reduced risk of hospital-acquired infection in LMIC (RR 0.50, 95% CI 0.36 to 0.71; *N* = 697 in 3 studies) Increased early growth: increased rate of length gain (MD 1.22 mm per wk, 95% CI 1.01 to 1.44; *N* = 320 in 5 studies), head circumference (MD 0.45 mm per wk, 95% CI 0.19 to 0.70; *N* = 320 in 5 studies), weight gain (MD 2.55 g/kg/d, 95% CI 1.76 to 3.34; *N* = 379 in 6 studies), and weight gain at 28 d in LMIC (SMD 1.57, 95% CI 0.79 to 2.36; *N* = 192 in 2 studies)

ASQ, Ages and Stages Questionnaire; BSID, Bayley Scales of Infant Development; CI, confidence interval; HIC, high-income country; MD, mean difference; OR, odds ratio; RR, risk ratio; SMD, standard mean difference; SR, systematic review.

prevent stunting, being underweight, and respiratory infections.[93] Supplementary feeding for healthy but socioeconomically disadvantaged children <5 years old in LMIC improves hemoglobin, growth, and psychomotor development,[94] but reported effects on cognition were mixed.[94] Chronic protein and caloric deficits during acute malnutrition lead to stunting and wasting and contribute to suboptimal neurodevelopment, and treatment with specially formulated therapeutic foods can facilitate recovery.[95,96]

Infection Prevention and Control During Childhood

Strategies for preventing and mitigating childhood infection are essential to optimizing child health and development (Table 6). Routine childhood vaccines are effective in reducing both morbidity and mortality, particularly from measles,[97] diarrhea,[98] and pneumonia.[99]

Interventions that improve the uptake of clean water, sanitation infrastructure, and optimal hygiene practices can prevent diarrhea and other water-borne diseases and reduce environmental enteropathy,[36] although there are few direct measures of developmental benefits. Promotion of optimal hand-washing and water quality-improvement strategies can improve weight for age and height for age among girls[100] and reduce diarrheal morbidity,[101] with some evidence of gains in development quotients at 5 to 7 years (See Supplemental Table 9).

Zinc as a diarrhea treatment can improve growth[102] and reduce persistent diarrhea.[103] Zinc supplementation among healthy children can mitigate the severity of diarrhea, reduce zinc deficiency, and increase height and weight.[104] Gogia and Sachdev[105] conducted a review of the effect of zinc supplementation on mental and motor development in children and concluded that there was insufficient evidence of developmental benefits in young children.

Intermittent preventive treatment among children who live in malaria-endemic areas can prevent severe malaria and anemia[106] and improve hemoglobin[107] in anemic children. A Cochrane review of deworming infected children showed improved growth, but presumptive treatment within population settings (such as mass deworming programs) has not been shown to have significant growth or developmental benefits,[108] which is a finding that is echoed by a recent network meta-analysis on mass deworming.[109]

TABLE 5 Review of Key Impacts for Nutrition Interventions Delivered During Infancy and Childhood

Key Interventions	Summary Effects With Implications for Developmental Outcomes (Direct Developmental Effects)
Breastfeeding promotion, 2 SRs, HIC, and LMIC	Improved breastfeeding practices from a variety of promotion interventions: more early initiation of breastfeeding in the first hour (OR 1.25, 95% CI 1.19 to 1.32; 49 studies), improved exclusive breastfeeding at day 1 (RR 1.43, 95% CI 1.09 to 1.87; *N* = 10 409 in 15 studies), in the first 6 mo (OR 1.44, 95% CI 1.38 to 1.51; 130 studies), and at 1–5 mo in LMIC (RR 2.88, 95% CI 2.11 to 3.93; 29 studies)
Iron supplementation, 2 SRs, HIC, and LMIC	Improved iron status with intermittent supplementation: reduced risk of anemia (RR 0.51, 95% CI 0.37 to 0.72; *N* = 1824 in 10 studies) and iron deficiency (RR 0.24, 95% CI 0.06 to 0.91; *N* = 431 in 3 studies) Mixed effects on development: improved motor quality (Behavior Rating Scale score MD 15.60, 95% CI 7.66 to 23.54; *N* = 172 in 1 study), improved psychomotor development (BSID II score MD 6.90, 95% CI 1.35 to 12.45; *N* = 172 in 1 study), reduced IQ (MD −3.00, 95% CI −5.96 to −0.04; *N* = 252 in 1 study), improved IQ (SMD 0.41, 95% CI 0.20 to 0.62; 9 studies), and improved mental development (combined score SMD 0.30, 95% CI, 0.15 to 0.46; 14 studies) Nonsignificant effects: motor development score (SMD 0.09, 95% CI −0.08 to 0.26; *N* = 1246 in 10 studies)
MMN supplementation, 3 SRs, HIC, and LMIC	Improved iron status: reduced risk of anemia (RR 0.66, 95% CI 0.57–0.77; *N* = 2524 in 11 studies), iron deficiency anemia (RR 0.43, 95% CI 0.35 to 0.52; *N* = 1390 in 7 studies), and improved hemoglobin (SMD 0.98, 95% CI 0.55 to 1.40; *N* = 8354 in 14 studies) Increased diarrhea: small significant increase in diarrheal risk (RR 1.04, 95% CI 1.01 to 1.06; *N* = 3371 in 4 studies) Small cognitive and motor benefits: improved academic performance at ages 5–16 (SMD 0.30, 95% CI 0.01 to 0.58; 4 studies) and motor development milestone score (MD 1.1, 95% CI 0.3 to 1.9; *N* = 361 in 1 study) Improved linear growth, weight gain, and hemoglobin was reported in 1 review with a low AMSTAR rating Nonsignificant effects: fluid intelligence (SMD 0.14, 95% CI −0.02 to 0.29; 12 studies) and crystallized intelligence (SMD −0.03, 95% CI −0.21 to 0.14; 11 studies)
Vitamin A supplementation, 1 SR, HIC, and LMIC	Improved vitamin A status: reduced risk of vitamin A deficiency (RR 0.71, 95% CI 0.65 to 0.78; *N* = 2262 in 4 studies), night blindness (RR 0.32, 95% CI 0.21 to 0.50; *N* = 22 972 in 2 studies), and xerophthalmia (RR 0.31, 95% CI 0.22 to 0.45; *N* = 57 866 in 2 studies) Reduced infectious disease morbidity: reduced incidence of diarrhea (RR 0.85, 95% CI 0.82 to 0.87; *N* = 37 710 in 13 studies), measles (RR 0.50, 95% CI 0.37 to 0.67; *N* = 19 566 in 6 studies), and malaria (RR 0.73, 95% CI 0.60 to 0.88; *N* = 480 in 1 study)
Complementary feeding education and provision, 1 SR, LMIC	Improved growth and nutrition status: reduced risk of stunting (RR 0.71, 95% CI 0.56 to 0.91; *N* = 1940 in 5 studies), and in food-secure populations improved height gain (SMD 0.35, 95% CI 0.08 to 0.62; 4 studies) and weight gain (SMD 0.40, 95% CI 0.02 to 0.78; 4 studies) Improved growth and nutrition status: reduced risk of stunting (RR 0.33, 95% CI 0.11 to 1.00; *N* = 1652 in 7 studies) and being underweight (RR 0.35, 95% CI 0.16 to 0.77; *N* = 319 in 12 studies) in food-insecure populations Reduced risk of respiratory infections (RR 0.67, 95% CI 0.49 to 0.91; *N* = 823 in 3 studies)
Supplementary feeding, 1 SR, HIC, and LMIC	Improved iron status in LMIC: increased hemoglobin (SMD 0.49, 95% CI 0.07 to 0.91; *N* = 300 in 5 studies) Improved growth and nutrition status in LMIC: increased weight-for-age *z* score (MD 0.15, 95% CI 0.05 to 0.24; *N* = 1565 in 8 studies) and height-for-age *z* score (MD 0.15, 95% CI 0.06 to 0.24; *N* = 4544 in 9 studies) Mixed effects on development in LMIC: increased psychomotor development score (SMD 0.41, 95% CI 0.10 to 0.72; *N* = 178 in 2 studies), reduced cognitive development score (SMD −0.40, 95% CI −0.79 to 0); *N* = 113 in 1 study), and increased cognitive development test battery score (SMD 0.58, 95% CI 0.17 to 0.98; *N* = 99 in 1 study)
Therapeutic foods for moderate and severe acute malnutrition, 2 SR, LMIC	Improved growth rate with therapeutic foods: increased rate of height gain (MD 0.14 mm per d, 95% CI 0.05 to 0.22; 3 studies), rate of weight gain (MD 1.27 g/kg per d, 95% CI 0.16 to 2.38; 3 studies) in severe acute malnutrition, and rate of mid-upper arm circumference gain in moderate acute malnutrition (MD 0.04 mm per d, 95% CI 0.02 to 0.06; *N* = 4568 in 4 studies)

BSID II, Bayley Scales of Infant Development, Second Edition; CI, confidence interval; HIC, high-income country; MD, mean difference; OR, odds ratio; RR, risk ratio; SMD, standard mean difference; SR, systematic review.

DISCUSSION

This overview has several limitations inherent to the search strategy that was used, and as such, it cannot comprehensively represent the full extent of the potential impact of MNCH&N interventions on child development. Studies that contributed to the pooled estimates reported here were selected on the basis of the included systematic reviews, which may not have focused on developmental impacts. We mitigated this by specifically scanning for and including developmental impacts that were not reported in the main reviews. We do recognize that incomplete reporting of study characteristics at the review level may have excluded potentially relevant study-level data.

Despite the large volume of the literature reviewed, and although effects on anthropometry, morbidity, and survival were consistently reported, our analysis shows a remarkable paucity of the direct measures of child development outcomes reported in both reviews and studies of interventions, which would plausibly have developmental impacts. In many instances, this could be related to study designs, primary objectives, and the duration of follow-up. For example, studies of asphyxia prevention and management typically only assessed outcomes in the short-term, such as neonatal mortality, hypoxia, and encephalopathy. In other cases, the

TABLE 6 Review of Key Impacts for Infectious Disease Prevention and Treatment Delivered During Infancy and Childhood

Key Interventions	Summary Effects With implications for Developmental Outcomes (Direct Developmental Effects)
Rotavirus, *H. influenzae* B, pneumococcal vaccines, and routine immunization, 2 SRs, LMIC	Reduced diarrheal morbidity: rotavirus vaccine reduced risk of severe rotavirus infection (RR 0.39, 95% CI 0.25 to 0.62; *N* = 1081 in 1 study) and severe gastrointestinal infection (RR 0.68, 95% CI 0.57 to 0.81; *N* = 2901 in 6 studies) Reduced pneumonia morbidity: HiB and pneumococcal vaccine reduced risk of clinically severe HiB pneumonia (RR 0.94, 95% CI 0.89 to 0.99; *N* = 5304 in 3 studies) and radiologically confirmed pneumococcal pneumonia (RR 0.74, 95% CI 0.63 to 0.88; *N* = 1619 in 3 studies)
Improved water, sanitation, and hygiene, 2 SRs, LMIC	Improved growth in girls: increased weight-for-age *z* score (MD 0.11, 95% CI 0.01 to 0.21; *N* = 2283 in 7 studies) and height-for-age *z* score (MD 0.15, 95% CI 0.04 to 0.26; *N* = 2283 in 5 studies) in girls only Water quality improvement: reduced diarrheal morbidity in children <5 y (RR 0.60, 95% CI 0.44 to 0.81; *N* = 5682 in 29 studies) Hand-washing with soap: reduced diarrheal morbidity (RR 0.53, 95% CI 0.37 to 0.76; *N* = 1896 in 7 studies) Excreta disposal: reduced diarrheal morbidity (RR 95% CI 0.37 to 0.92; 4 studies)
Zinc supplementation and diarrhea treatment, 5 SRs, HIC, and LMIC	Improved growth: increased height gain (SMD 0.19, 95% CI 0.08 to 0.30; 34 studies), height (SMD 0.09, 95% CI 0.06 to 0.13; *N* = 13 669 in 50 studies) and weight gain (SMD 0.10, 95% CI 0.07 to 0.14; *N* = 12 305 in 44 studies) Improved zinc status but lowered iron status: reduced zinc deficiency (RR 0.49, 95% CI 0.45 to 0.53; 15 studies) and reduced serum ferritin (SMD −0.07, 95% CI −0.13 to 0.00; 18 studies) Mixed effects on respiratory infection prevalence, more vomiting: increased lower respiratory tract infection prevalence (RR 1.20, 95% CI 1.10 to 1.30; 3 studies), decreased pneumonia morbidity (RR 0.81, 95% CI 0.73 to 0.90; 6 studies), and more vomiting episodes (RR 1.68, 95% CI 1.61 to 1.75; *N* = 4095 in 5 studies) Reduced infectious disease morbidity: lower incidence of diarrhea (RR 0.87, 95% CI 0.81 to 0.94; 14 studies), persistent diarrhea (RR 0.73, 95% CI 0.62 to 0.85; 8 studies), and severe diarrhea (RR 0.89, 95% CI 0.84 to 0.95; 6 studies) Less diarrhea, more vomiting: reduced duration of persistent diarrhea (MD −15.84 h, 95% CI −25.43 to −6.24; *N* = 529 in 5 studies) and increased risk of vomiting (RR 1.59, 95% CI 1.27 to 1.99; *N* = 5189 in 10 studies) Nonsignificant effects: mental development score (MD −0.5, 95% CI −2.06 to 1.06; *N* = 2134 in 8 studies) and psychomotor development score (MD 1.54, 95% CI −2.26 to 5.34; *N* = 2134 in 8 studies)
Intermittent preventive therapy and bed nets, 2 SR, LMIC	Improved hemoglobin status: during intervention, reduced risk of severe anemia (RR 0.24, 95% CI 0.06 to 0.94; *N* = 3282 in 2 studies) and moderately severe anemia (RR 0.71, 95% CI 0.52 to 0.98; *N* = 8805 in 5 studies), and higher change in hemoglobin at 12 wk follow-up (MD 0.32 g/dL, 95% CI 0.19 to 0.45; *N* = 1672 in 4 studies) Reduced malaria morbidity: reduced risk of severe malaria (RR 0.27, 95% CI 0.10 to 0.76; *N* = 5964 in 2 studies) and clinical malaria (RR 0.26, 95% CI 0.17 to 0.38; *N* = 9321 in 6 studies)
Deworming drugs, 1 SR, LMIC	Improved anthropometric measures: treatment of infected children increased weight (MD 0.75 kg, 95% CI 0.24 to 1.26; *N* = 627 in 5 studies), height (MD 0.25 cm, 95% CI 0.01 to 0.49; *N* = 647 in 5 studies), and mid-upper arm circumference (MD 0.49 cm, 95% CI 0.39 to 0.58; *N* = 396 in 4 studies)

CI, confidence interval; HiB, *Haemophilus influenzae* B; HIC, high-income country; MD, mean difference; RR, risk ratio; SMD, standard mean difference; SR, systematic review.

dearth of developmental measures is potentially related to the difficulty in assessing such outcomes in addition to mortality and morbidity. The available evidence suggests that benefits to development can be derived from maternal and child nutrient supplementation and protective interventions for at-risk infants both before and after birth. In fairness, most interventions are implemented for direct benefits on child survival, and this is sufficient rationale to provide them. However, there is insufficient information on whether a reduction in mortality in a population with a given health and nutrition intervention also reduces the incidence of severe morbidities, subsequent developmental deficits, or the converse. Even in those reviews that do have meta-analyses of effects on cognitive or motor development, relatively few studies are included, hence our effort at collating the evidence from individual studies that were reported outside meta-analyses.

Research Gaps

There is currently no global set of standard indicators for the measurement of child development,[110] and few direct measures of child development have actually been validated in the LMIC with the highest burdens of undernutrition and developmental delay.[111] Longitudinal data collection in a broader set of countries is needed to quantify the social and economic benefits of MNCH&N interventions, including those deriving from averted developmental delays.[112] Mainstreaming the collection and reporting of child development outcomes for interventions that have a plausible link to developmental processes is needed. Some interventions may confer additional developmental benefits alongside those that are mediated through improved nutrition and reduced infectious disease burden, and they cannot be captured solely through typical anthropometric or clinical measures. A key example is KMC for preterm infants, which can reduce mortality, infection, and hypothermia in addition to improving breastfeeding practices[31] (and so addressing multiple risk factors simultaneously). The recently updated Cochrane review on KMC[113] shows a 50% reduced risk of severe infection or sepsis (risk ratio 0.50, 95% confidence interval 0.36 to 0.69; *N* = 1463 in 8 studies). Whereas KMC could affect development through mitigating infection and improving nutrition, improved mother-infant attachment[68] suggests additional

benefits could be mediated through stimulation and early socioemotional development. Infant massage and emollient therapy are other neonatal interventions with stimulation components that require additional research to determine their effectiveness, particularly in LMIC.

Implications for Policy and Research

The benefits of maternal health and nutrition interventions in pregnancy for both mother and infant are well established. The consequences of IUGR for child growth and development are myriad and include neurodevelopmental deficits, poorer school performance, and behavioral issues in childhood.[114] At least one-fifth of all stunting at 6 months is determined by fetal malnutrition and SGA.[37] Prevention and early detection of IUGR to institute interventions may mitigate detrimental effects on the developing fetus.[21] Limited available evidence suggests that interventions addressing maternal undernutrition and micronutrient deficiencies should start early and preferably before conception.[55] Whereas supporting maternal mental health is essential, antidepressant use during pregnancy may increase the risk of poorer birth outcomes.[115,116] Perinatal psychosocial support and counseling provided to mothers can be successfully delivered in low-resource settings.[117] Additional research is also needed to understand the effects of violence and stress on maternal mental health and subsequent effects on child development (particularly in conflict zones) so that targeted interventions can be developed.

The findings of this overview further strengthen recommendations for the scale-up of both nutrition and infection prevention and treatment interventions delivered during the prenatal and immediate neonatal period to support both child survival and optimal development.[36] Childbirth and the immediate neonatal period present a variety of risks to both mother and child, particularly for infants who are born preterm or SGA and those without access to skilled birth attendance. Recent evidence from rural Nepal (a setting with extremely low coverage of skilled birth attendance) demonstrated a significant association between SGA and low birth weight and poorer neurocognitive outcomes.[118] In a high-income setting, moderate preterm birth combined with SGA has been associated with general cognitive deficits in adolescents 18 years later, although the study subgroup size was small.[119,120] Links between preventable intrauterine and neonatal disease and neurodevelopmental outcomes have also been demonstrated, with preterm birth and neonatal sepsis being associated with substantially increased risk of ≥1 neurocognitive or motor deficit.[23]

There exists ample evidence supporting the benefits of breastfeeding, yet global coverage of this intervention remains low with little change over time. Implementing breastfeeding promotion and support strategies also necessitates investments in strategies to secure appropriate maternity leave, supportive work environments, and protection of this precious public health intervention from inappropriate marketing of breast milk substitutes. Further highlighting the critical role of nutrition in early developmental processes are recent findings from the Pelotas birth cohort in Brazil, where 30 years later, breastfeeding was found to be associated with intelligence and educational attainment.[120] A large-cluster randomized trial of breastfeeding promotion using the Baby-Friendly Hospital Initiative model in Belarus found that this intervention significantly increased verbal IQ at 6.5 years.[82] Recent meta-analyses of the effect of a variety of macronutrient and micronutrient supplementation programs in children showed small but significant effects on mental development whereas stimulation interventions have shown greater effect sizes,[121] which suggests that delivering nutrition interventions alone may be insufficient. These data collectively reinforce the potential integration of early child health and nutrition interventions with strategies such as stimulation and responsive feeding to optimize development outcomes.

Panel: Recommended Core Package of MNCH&N Interventions and Actions to Support Child Development

1. During preconception and pregnancy:
   a. improve nutritional status with micronutrients as a supplement to a diverse and calorically adequate diet
   b. reduce the risk of infection with screening, treatment, and prophylaxis
   c. support maternal mental health and well-being by addressing domestic violence and preventing and treating depression
2. During labor, child birth, and the immediate neonatal period:
   a. ensure access to a safe, hygienic birth and essential newborn care
   b. mitigate the effects of preterm birth and complications with neuroprotective interventions and KMC
   c. promote early and exclusive breastfeeding
3. During infancy and early childhood:
   a. promote and support optimal breastfeeding and responsive complementary feeding practices coupled with adequate psychosocial stimulation (eg, the Care for Child Development package)

b. provide micronutrients for children at risk for deficiency

c. reduce infectious disease morbidity through screening, treatment, and prophylaxis

d. support access to safe water and sanitation facilities, and promote hygienic behaviors for mothers and children

4. Future research on early interventions should prioritize follow-up in early childhood and measure developmental progress whenever possible

5. Encourage intersectoral cooperation throughout the continuum of care, and support the concurrent delivery of both life-saving and brain-saving interventions (such as packages of care) in each of these critical windows

Recommendations for Integrated Implementation and Research

Of the existing interventions, those that are recommended for scaling-up are cost-effective packages of care to enhance adolescent and young women's nutrition and health status complemented with continued preventive and protective interventions during pregnancy. The findings that MMN supplementation is associated with greater benefits than traditional iron-folic acid therapy predicate a concerted move to scale these up for global use. Similarly, supporting food-insecure and actively malnourished women with proper supplements or food baskets is not only a humanitarian imperative; the benefits to maternal health and infant outcomes are considerable. The period from birth to 2 years is a particularly crucial time to intervene and set children on optimal developmental trajectories and affords the ability to integrate the implementation of complementary actions that support nutrition and stimulation. Interactions with the health sector offer unique opportunities for promoting early child development, and this is leveraged in the United Nations Children's Fund's Care for Child Development Package.[122] Such strategies for integrating early child health, nutrition, and stimulation interventions through community health workers have been successful in rural Pakistan.[123,124]

Overall, the evidence supports existing recommendations for a scale-up of interventions across the continuum of care to reduce mortality and morbidity and for potential benefits to children's cognitive, motor, and socioemotional development. Maintaining an equity focus and targeting specific at-risk populations with both prevention and treatment (eg, undernourished mothers, preterm infants, anemic infants, and rural and underserved populations) is necessary to have maximum impact. Additional research attempting to quantify developmental impacts would strengthen current recommendations and provide governments with additional economic incentives to invest in MNCH&N.

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ABBREVIATIONS

AMSTAR: A Measurement Tool to Assess Systematic Reviews
IUGR: intrauterine growth restriction
KMC: Kangaroo Mother Care
LMIC: low- and middle-income countries
MMN: multiple micronutrient
MNCH&N: maternal, newborn, and child health and nutrition
SGA: small for gestational age

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