Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Leila Margaret Larson Date

The consequences of malnutrition, and effects of multiple micronutrient powders, on young child development in India

By

Leila Margaret Larson
Doctor of Philosophy (Candidate)
Nutrition and Health Sciences
Laney Graduate School

_____	_____
Dr. Reynaldo Martorell, Ph.D. Advisor	Dr. Patricia Bauer, Ph.D. Committee Member
_____	_____
Dr. Lynnette Neufeld, Ph.D., M.S. Committee Member	Dr. Usha Ramakrishnan, Ph.D., M.S. Committee Member
_____	_____
Dr. Amy Webb Girard, Ph.D. Committee Member	Dr. Melissa Fox Young, Ph.D. Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

The consequences of malnutrition, and effects of multiple micronutrient powders, on young child development in India

By

Leila Larson

B.A.Sc., University of British Columbia, 2010

M.P.H., Columbia University, 2013

Advisor: Dr. Reynaldo Martorell, Ph.D.

An abstract of

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Nutrition and Health Sciences

2017

Abstract

The consequences of malnutrition, and effects of multiple micronutrient powders, on young child development in India

By Leila Margaret Larson

Nutrition plays an important role in the growth and development of a child, particularly in low- and middle- income countries where malnutrition is often widespread. Nutrition programs, especially in children under two years of age, have the potential to improve the mental developmental of at-risk populations. This dissertation uses data from a two-arm randomized cluster effectiveness trial of home fortification with multiple micronutrient powders (MNPs) in children 6-18 months of age living in rural Bihar, India. Objectives were to examine 1) the nutritional, psychosocial, environmental, and household correlates of child development, and identify mediators between dietary diversity and mental development, 2) the impact of home fortification with MNPs on motor and mental development, memory, and executive function, and 3) a path analysis of the relations between diet, hemoglobin, nutritional status, motor development, stimulation and various cognitive domains. Results identified length-for-age z-scores (LAZ), dietary diversity, and psychosocial stimulation as significant predictors of motor and mental development. Further, stimulation, gross motor development, and fine motor development were significant mediators in the relation between dietary diversity and mental development. Results of the impact evaluation indicate that children who received MNPs and whose caregivers received nutrition counseling performed better on tests of motor and mental development than children whose caregivers received nutrition counseling only. We also found greater impacts of MNPs on motor and mental development in children from households with higher stimulation scores at baseline compared to those from households with lower stimulation scores at baseline. Lastly, the path analysis indicated significant direct and indirect associations between LAZ, motor development and personal social skills, language development, memory, and executive function. Stimulation was significantly associated with language abilities, and hemoglobin concentrations with memory. The findings from this dissertation suggest that nutrition indicators, such as dietary diversity and LAZ, are important predictors of early child development, and could influence cognitive abilities through motor development and psychosocial stimulation. Programs addressing both stimulation and nutrition could have important impacts on child development. In this context, despite low coverage and overworked frontline health workers, home fortification with MNPs was found to have modest effects on early child development.

The consequences of malnutrition, and effects of multiple micronutrient powders, on young child development in India

By

Leila Larson

B.A.Sc., University of British Columbia, 2010

M.P.H., Columbia University, 2013

Advisor: Dr. Reynaldo Martorell, Ph.D.

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Nutrition and Health Sciences

2017

Acknowledgements

First, I would like to thank my advisor, Dr. Reynaldo Martorell, for his guidance, kind words, and use of informative idiomatic expressions over the past four years. Dr. Martorell has been a consistent source of support and positivity throughout this influential time, and working with him has been a rewarding experience. I am grateful for his contributions to my professional growth. I thank Dr. Patricia Bauer for encouraging me to bridge the fields of nutrition and child psychology. I thank her for building my research skills, for believing in my ideas and decisions, and for reminding me not to take life too seriously. I am grateful to Dr. Lynnette Neufeld for being my strong female mentor. I thank her for taking me under her wing and imparting a valuable slice of her experience. Our conversations left me confident to take on the next challenge. I thank Dr. Usha Ramakrishnan for her support throughout my time at Emory, in navigating the NHS program, and encouraging my professional development. I thank Dr. Melissa Young for her support and kindness throughout many experiences here and abroad. I thank Dr. Amy Webb Girard for mentoring me professionally while keeping me in shape physically. She was my sounding board on many pivotal occasions. Lastly, I want to thank my family, friends, and better half (Saam Batmanghelidj), who never let me doubt myself.

Dedication

I dedicate this dissertation to my parents, Dr. Frances Aboud and Dr. Charles Larson. With their guidance and support, I have developed a fulfilling professional and personal life. They taught me to be curious, challenge myself, problem solve, and pursue all dreams. I aspire to achieve their passion for career and life. I thank them for believing in me unwaveringly.

List of abbreviations

ASHA	Accredited Social Health Activist
ARA	Arachidonic acid
AWC	Anganwadi Center
AWW	Anganwadi Worker
BMI	Body mass index
BSID	Bayley Scales of Infant and Toddler Development
CFI	Comparative fit index
DFS	Double fortified salt
DHA	Docosahexanoic acid
DMC	Developmental Milestones Checklist
ECDI	Early Child Development Index
EEG	Electroencephalography
EFF	Encapsulated ferrous fumarate
EPHPP	Effective Public Health Practice Project
FCI	Family Care Indicators
FLW	Frontline health worker
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAZ	Height-for-age z-score
HSC	Health sub-center
ICDS	Integrated Child Development Services
IFA	Iron folic acid
IFHI	Integrated Family Health Initiative
INCAP	Institute of Nutrition of Central America and Panama
IUGR	Intrauterine growth restriction
IYCF	Infant and young child feeding
LAZ	Length-for-age z-score

LMIC	Low- and middle-income country
MNP	Multiple micronutrient powder
MUAC	Mid-upper am circumference
NFHS	National Family Health Survey
NMDA	N-methyl-D-aspartate
PDS	Public Distribution System
RCT	Randomized controlled trial
RMSEA	Root mean square error of approximation
SEM	Structural equation model
SQ-LNS	Small-quantity lipid-based micronutrient supplements
SRS	Simple random sample
TLI	Tucker Lewis Index
WHO	World Health Organization
WLZ	Weight-for-length z-score

Table of Contents

Table of Tables

Table of Figures

Chapter 1: Introduction

Estimates indicate that 250 million, or 43%, of children under five years of age worldwide fail to fulfill their developmental potential (1). The consequences of poor early child development are considerable and long-lasting, with the potential to influence the cognitive performance and earning potential of current and subsequent generations. Evidence to date indicates that nutrition and stimulation interventions provided to children exposed to resource-limited environments can have beneficial effects on short-term cognitive and behavioral development (1), but also on their later life earning potential (2), school attainment (3), competence (4), and offspring growth (5, 6). Impact varies by type of intervention, the context, and the population. Efforts are being made to determine how to most effectively intervene and improve development on an individual and population level.

Due to the devastating consequences and the potential for remediation, promising evidence from research on child development and from interventions aimed to improve early development have been effective in mobilizing interest and funds (7). The increased interest and funding may explain in part why the number of publications related to early child development have increased over the past decade (by a factor of two for studies of the impact of micronutrients and a factor of three for stimulation studies) (1). Global public health agencies (such as the World Health Organization), governments, and non-governmental organizations are interested in evidence-based cost-effective decision making and know that investment in effective programs can have important implications for the economy and well-being of a country. Thus, researchers continue to summarize what is currently known about effective programs and

to evaluate new avenues for interventions. In parallel are efforts to understand how our interventions are actually influencing the mental development of children.

There is compelling evidence, both from animal and human studies, for a sensitive period during which interventions have the largest impact on child development, in other words, a window of sensitivity. The brains of infants and toddlers undergo rapid structural and functional changes throughout the first few years of life. Their brains are malleable and so are able to overcome or compensate for insults, such as nutritional deficits or stressful events. Supporting evidence comes from adoptions studies. For instance, Korean children adopted to middle-class American families before the age of two years performed better on intelligence quotient tests than children adopted after the age of two years (8). Similarly, studies in Romanian orphanages show that the later an orphan was taken out of institutional care, the worse they performed on cognitive tests (9-12). Younger children demonstrate an ability to reorient their developmental trajectory, after being exposed to physical or psychological stress more easily than older children (13, 14).

Humans have substantially larger brains than other primates do. Our brains are composed of 16 billion neurons, compared to 9 billion for our close relatives (other primates, eg., the gorilla) (15). From birth to approximately age three years, 700 neural connections develop every second. An overproduction of neurons in this age range allows an infant to adapt to many environments; once settled into a particular environmental niche, pruning of neurons to reduced unused pathways begins. In infancy and childhood, the brain thereby becomes specialized for selected environments, something that becomes more difficult in adulthood. It is because of the brain's plasticity during this window that it is most advantageous to intervene in early life. At this stage, the brain is sensitive to enrichment, but also to insult. It is also a stage at which

humans are wholly dependent on their parents, or caregivers. Therefore, interventions to enhance child development should target the young child, whose brain is sensitive, and also the parent, whose nurturing is vital to the child's survival and development.

As children age, unused brain synapses are gradually deleted. This may be useful as the brain specializes for the selected context, but it may be an impediment if context-relevant input is absent. Recovery of useful synapses is possible, but at additional costs. For instance, children who do not build a good vocabulary in early years have difficulty learning how to read (16). Similarly, math concepts are more difficult for children who do not build problem-solving abilities in the first few years (16). Lastly, children with poor emotional attachment in early life find it difficult to cope with stressful and difficult situations throughout life. It is within this window of opportunity that stimulation and nutrition interventions in resource-limited settings have had the largest potential to benefit.

Nutrition has proven to be an important predictor of development, and interventions to address malnutrition in many low- and middle-income countries (LMICs) have improved children's short- and long-term development. The consistent effects of nutrition in childhood have been well demonstrated in one of the longest nutrition intervention follow-up studies, the Institute of Nutrition of Central America and Panama (INCAP) study (17). As part of a cluster randomized study, Guatemalan children under seven years of age received a highly nutritious supplement and controls received a placebo, with the primary aim of examining effects on development (17). In adolescence, those in the intervention group scored higher on tests of knowledge, numeracy, reading, vocabulary, and information processing (18). Between 25-42 years of age, those who had received the supplement as children had higher completed grades of school and performed better on reading comprehension and cognitive tests (3). Further, males

exposed to the supplement before three years of age had higher hourly wages (19). This study paints a promising picture of the substantial impact an early nutrition intervention can have throughout life. It spawned a number of nutrition interventions aimed at determining the kinds of nutrients children needed to enhance a variety of different mental abilities, and at which ages. The present dissertation addresses still important gaps in the literature by examining the effects of a micronutrient intervention on child development, and by exploring how nutrition and other inputs, such as stimulation, contribute to different mental abilities in young children.

1.1 Aims

The aims of this thesis are as follows:

1. Review the evidence for the effect of nutrition supplementation on mental development of children under two years of age in LMICs.

Chapter 3: We performed a review and meta-analysis of the effects of macronutrient and micronutrient supplementation trials on mental development in children under two years of age living in LMICs. We also examined the proposed pathways by which nutrition may impact mental development, namely nutritional status and motor development.

2. Examine nutritional, psychosocial, environmental, and household correlates of motor and mental development, and identify mediators of the relation between diet and mental development in infants and young children.

Chapter 4: We used cross-sectional baseline data from a nutrition intervention in children 6-18 months of age in Bihar India, to establish associations between nutritional, psychosocial,

environmental, and household characteristics and early child development. We also examined potential mediators between dietary diversity and mental development.

3. Examine the impacts of home fortification with multiple micronutrient powders (MNPs) on motor and mental development, executive function, and memory of children.

Chapter 5: We use data from a two-arm cluster effectiveness trial in 70 health sub-centers in Bihar, India, randomized to receive either MNPs and nutrition counseling (intervention) or nutrition counselling alone (control) for 12 months. Effects on motor and mental development, executive function, and memory were examined in children 6-18 months of age.

4. Construct and test a theoretical model looking at the associations between diet, hemoglobin, length-for-age z-scores (LAZ), motor development, stimulation, and an array of cognitive domains (language, personal-social development, memory, and executive function) in infants and young children.

Chapter 6: We performed structural equation modeling using cross-sectional endline data from a nutrition intervention in rural Bihar, India, to examine a theoretical model looking at the associations between diet, hemoglobin, LAZ, motor development, stimulation, and an array of cognitive domains in children 12-18 months of age.

Chapter 2: Literature review

This literature review begins with an overview of the role of micronutrients on child development, drawing mainly from animal studies because the biological mechanisms are more difficult to study in humans. Then, I discuss the research from randomized trials in humans

looking at the effects of nutrition on child development. The review focuses, but is not limited to, micronutrients to review the literature that best informs my dissertation. Finally, I review the evidence for mediators in the relation between nutrition and child development. The purpose of outlining the mediating pathways is to draw attention to factors that reduce or enhance the effects of nutrition on development.

2.1 Micronutrients and how they affect child development

Micronutrients play an important role in the structural and functional development of the brain. Evidence for the role of nutriton at the cellular and molecular level is primarily available from animal studies. Though many of these processes translate to humans, it is important to acknowledge that the associations seen in animals may not be directly applicable to the developing human brain. The first 1000 days of life is a period of rapid brain development and a prime time to intervene. As areas of the fetal and infant brain develop, the timing of deficiency can interupt time-sensitive processes (20). For instance, the neural plate and neural tube develop as early as 22 days after conception. Their proper formation is highly dependent on micronutrients such as folic acid, copper, and vitamin A (21). If deficiencies in these micronutrients exist at this time, there may be irreparable damage to the neural tube resulting in lifelong defects. Although there is clear evidence for the role of micronutrients on brain development, the extent to which deficiencies will cause harm or damage is not well understood, nor is the extent to which micronutrient interventions lead to recovery or prevent developmental deficits. This section outlines the role of key micronutrients and fatty acids on brain development.

2.1.1 Iron

Nearly 20% of preschool-aged children in low- and middle-income countries (LMICs) are iron deficient, and 25% of anemia is associated with iron deficiency (22). Even before birth, many children are exposed to iron deficiency caused by poor maternal iron status, intrauterine growth restriction (IUGR), and gestational diabetes mellitus, health issues that are also present in high-income countries. Maternal hypertension, which causes IUGR, restricts the blood flow of iron. The remaining iron is prioritized by red blood cells and less reaches the brain. Maternal diabetes mellitus leads to chronic fetal hyperglycemia and hyperinsulinemia. The hypoxic environment means that more iron is needed for hemoglobin synthesis, resulting in fetal iron deficiency. Similar to IUGR cases, iron is prioritized to red blood cells rather than the brain. Nelson et al investigated the short and long term effects of an early hypoxic environment by studying memory in infants of diabetic mothers. As neonates, these infants showed reduced recognition memory compared to infants of non-diabetic mothers (23). These deficits were still apparent in 12 and 30 month olds, in tasks of memory and overall motor and mental development using the Bayley Scales of Infant and Toddler Development (BSID) (23). Scores on tasks of memory in newborns were also correlated with their ferritin concentrations (23). The influence of iron on neurodevelopment has been studied extensively because of iron's role in neurochemistry, neurometabolism, and neuroanatomy in infancy and early childhood across populations (24). Further, iron plays an important role in oxidative energy production, transporting oxygen, and facilitating oxygen's use in energy transfer (25). Iron is found in hemoglobin, myoglobin, enzymes, and respiratory chain proteins (25).

Animal studies have demonstrated iron's role in myelination, neurotransmission, dendritogenesis, and synaptogenesis. Most of the research has focused on two important regions of the brain, the striatum and the hippocampus. The striatum is related to higher order cognitive and emotional functions, memory, behavior, and motor functioning; the hippocampus is vital for recognition memory and learning, and other important functions and behaviors such as anxiety and depression. Animal models have shown that the fatty acid composition and synthesis of myelin is altered in the presence of iron deficiency (26-29). In fact, 70% of brain iron is associated with myelin (30). White matter in young rats is significantly reduced with iron deficiency at 21 days, becoming worse as the deficiency continues (31). Dopamine, serotonin, norepinephrine, monoamines, and iron are consistently correlated in the brain, and effects of iron repletion in young rodents persists into adulthood (32-37). Specific alteration of the neurostriatal neurons caused by iron deficiency has negatively affected fine motor, gross motor, motor sequencing, and sensory abilities in rats (36). Synaptic efficiency and maturity is reduced in rodents exposed to gestational and early postnatal iron deficiency (38). Structural alterations due to iron deficiency in early life include less linear dendritic growth and more tangled dendritic branches, which were also evident in adulthood (38). The extent of disruption on neurodevelopment depends on the timing and duration of iron deficiency. For instance, transient reductions in iron status have been shown to alter monoaminergic neurotransmission, but did not show changes in brain iron levels (39). Structural, dopaminergic, neurometabolic, neurochemical, and electrophysiologic functions in the striatum and hippocampus have been shown to be affected by iron deficiency in rats including grooming behavior, forelimb activity, reduced exploration of novel environments, drowsiness, decreased attention and learning (40), and recognition memory (41-44).

2.1.2 Iodine

Iodine is essential for the synthesis of thyroid hormones, which are used in neurogenesis and are vital for maturation of the central nervous system (45). In the absence of thyroid hormones, the central nervous system undergoes irreversable morphological and biochemical changes that lead to mental retardation (17). Deficiency during gestation results in reduced axon growth and dendritic branching in the cortex (46). It also negatively affects the migration of radial neurons, which settle permanently in heterotopic locations within the cortex and hippocampus (46). Long-term effects are seen from gestational iodine deficiency on synaptic density, neurotransmitter and neuropeptide levels (norepinephrine, dopamine, etc.), and neurotransmitter enzyme activity (34, 45). Similarly, it causes reduced deposition of myelin and delays the development of myelin-associated enzymes (45-47). A meta-analysis of iodine and mental development in children under five years of age concluded that iodine deficient children scored 7 to 10 points lower on developmental quotient tests than iodine sufficient children (48).

2.1.3 Zinc

Zinc is important for growth because of its role in the activity of insulin-like growth factor 1 (49). It also has a role in DNA, RNA (50-52) and protein (53) synthesis. Zinc is essential for proper brain development and function. Because of its role in cell division, rodents exposed to gestational zinc deficiency show reduced brain DNA and total brain mass in the cerebellum, limbic system, and cerebral cortex (54-56), in addition to decreased arborization of dendritic branches (57). Zinc deficiency has been shown to affect hippocampal neuronal functioning (58).

Zinc can interact with neurotransmitter receptor proteins (52). Studies in rats demonstrate that zinc inhibits γ-aminobutyric acid receptor function in spinal cord neurons (59) as well as N-methyl-D-aspartate (NMDA) receptors in hippocampal neurons (60). Metallothionein is a zinc-binding protein in neurons, which acts as a free-radical scavenger and cleanses the body of toxic metals such as cadmium and mercury (52). Despite the benefits observed in animal studies, few randomized controlled trials (RCTs) in humans show significant effects of zinc supplementation on cognitive development. A recent review and meta-analysis of zinc supplementation trials in children under two years of age showed no trials with significant positive effects (61). However, one double-blind randomized trial in Dhaka, Bangladesh, reported a significant negative effect of zinc supplementation from 1-5 months of age on mental development as measured using the BSID-II (62).

2.1.4 B-vitamins

Early in gestation (weeks 2 to 4), the neural tube forms. The neural tube consists of progenitor cells which lead to neurons and glial cells. Folic acid and vitamin B12 are vital at this stage of fetal development; deficiency can lead to neural tube defects, most notably anencephaly and spina bifida (63). Vitamin B6 is another important B-vitamin for the developing central nervous system, and deficiency can have important effects on brain development and cognitive functions (64). Rodent studies determined that gestational and early postnatal vitamin B6 deficiency is associated with reduced dendritic branching in the developing cerebellum and neocortex (65, 66). Deficiency also has detrimental effects on synaptic density; it alters the efficiency NMDA receptors, and decreases dopamine levels and dopamine D2 receptor binding

(64, 66, 67). Finally, rats fed diets with lower amounts of vitamin B6 showed markedly less myelination than those fed more B6, with a clear dose response (68).

2.1.5 Fatty acids

Docosahexanoic acid (DHA), a long-chain omega-3 fatty acid, is thought to be essential to fetal and infant brain development and growth (69). It is highly concentrated in the brain, and its integral role in membrane lipids raises the possibility that inadequate DHA alters brain development through its effects on nerve impulse transmission, synaptogenesis, cell signal transduction and myelination (69, 70). Myelin is the lipid insulation layer of neuronal axons and deficits in myelination cause global brain dysfunction. Particularly during the third trimester and the first year of life, the developing brain is sensitive to variations in the supply of DHA, which is dependent on maternal diet for breastfed infants (71). In the recent DHA Intake and Measurement of Neural Development trial, infants were supplemented with DHA and arachidonic acid (ARA), an omega-6 fatty acid, at difference ratios. Children who received the supplement performed better on most developmental tasks between 4-72 months; however, many of the outcomes show a reduction of benefit from the highest DHA dose (DHA:ARA ratio of 1.5:1 compared to 0.5:1 and 1:1). Red blood cell data showed that increased DHA supplementation beyond 0.64% reduced ARA in the blood. Their findings suggest that the balance of DHA:ARA contributes to the effect of supplementation on child cognition (72).

2.2 Effect of nutrition on child development: evidence from randomized trials in humans

Systematic reviews and meta-analyses including randomized nutrition interventions with children under five years of age show mixed evidence for effects on mental development (73-75). A recent meta-analysis by Larson and Yousafzai focused on nutrition interventions with children under two years of age living in LMICs and concluded that there was a significant but small impact on mental development (overall effect size d=0.08) (61). However, when stratified by type of nutrition intervention, only macronutrient trials revealed a significant effect, whereas multiple and single micronutrient trials did not have an impact. In fact, the only multiple micronutrient trial which demonstrated a significant impact on mental development was a large effectiveness trial with Pakistani children from birth to 23 months of age (76). Compared to the standard nutrition education delivered by frontline health workers, enhanced nutrition (which included additional nutrition education for mothers with children 0 to 23 months and multiple micronutrient powders once children reached 6 months) resulted in improvements in cognitive, language and socio-emotional development at 12 months and improved language at 24 months (76). Children were again followed up at four years of age and benefits of enhanced nutrition were observed on pro-social behaviors and motor development, while effects on cognitive development were attenuated (77). Pasricha et al reviewed the effect of iron supplementation in children 4-23 months of age and found no differences in mental or motor development scores (78). Thompson et al reported a significant effect of iron supplementation on mental development in older children 2-5 years of age (79); however only two studies (80, 81) were included in this calculation and only one (81) of the two studies found significant impact. In a rural population of children with high anemia and infection, Stolzfus et al found that iron supplementation compared to placebo improved language development by 0.8 points; motor

development was improved only in children with hemoglobin concentration less than 9 g/dL (81). In summary, the systematic reviews of studies conducted before 2015 showed one multiple micronutrient study (76) with an impact and a handful of iron-only supplement studies (81-86) with an effect on mental development in children under two years.

A number of large-scale nutrition trials using multiple micronutrients have been conducted since the publication of Larson and Yousafzai's meta-analysis (61). Prado et al published three small-quantity lipid-based micronutrient supplements (SQ-LNS) trials in Sub-Saharan Africa. SQ-LNS provide a low dose (less than 120 calories/day) of energy, protein, macro-minerals and essential fatty acids, in addition to micronutrients. One cluster randomized trial in Burkina Faso found that children from communities who received SQ-LNS and treatment of malaria and diarrhea from 9 to 18 months of age showed improvements in motor (0.34 SDs higher), language (0.30 SDs higher), and personal-social (0.32 SDs higher) development compared to children from non-intervention communities (87). Two other trials in Malawi and Ghana used similar designs and provided SQ-LNS to mothers during pregnancy until 6 months postpartum and SQ-LNS to children 6 to 18 months of age compared to iron and folic acid (IFA) or multiple micronutrient supplementation to mothers only during pregnancy (88, 89). In Malawi, children from the SQ-LNS group showed earlier acquisition of gross motor milestones (walking alone, waving goodbye, and standing with assistance) (88). However, at 18 months of age, there were no differences in motor, language, socio-emotional development, or executive function (higher-order cognitive functions) between intervention groups (88). In Ghana, more children who had received SQ-LNS were able to walk at 12 months of age compared to the IFA group (89). Consistent with the Malawi trial, no improvements were seen at 18 months of age in motor, language, socio-emotion development, or executive function (89). This suggests an early

effect of maternal and child SQ-LNS supplementation on walking at 12 months, but no sustained effects on motor or mental development by 18 months of age at the end of the supplementation. Another SQ-LNS trial in Bangladesh supplemented mothers during pregnancy until 6 months postpartum with either SQ-LNS or IFA; children received either SQ-LNS, multiple micronutrient powders (MNPs), or no supplement from 6 to 24 months of age (90). At 18 months, children from all intervention groups showed improved motor skills compared to children who did not receive a supplement (and whose mothers received IFA) (90). At 24 months, children from intervention groups scored higher on receptive and expressive language scores, but not personal-social scores or executive function (90). In the latter trial, a parent-report measure was used to assess development, whereas in the former trials in Malawi and Ghana, a direct assessment of child abilities was used.

Because findings from recent nutrition trials are mixed, it is important to ask more specific questions about the conditions for effective interventions: What type of nutrition intervention is most effective in what contexts? At what age and for how long should nutrition supplementation be provided? Are effects seen in RCTs maintained in effectiveness trials? What is leading to the mixed effects seen to date? In the hopes of illuminating answers to some of these questions, in the next section, I examine the mediating pathways between nutrition supplementation and child development. The pathways through which nutrition can influence child development are varied and inter-related, and could help decipher why some trials see effects and others do not in different contexts and populations.

2.3 Conceptual framework for how nutrition improves child development

Pollitt and colleagues developed a conceptual framework for how nutrition relates to child development (91). Since then, he and others have tested its validity using study data in a range of settings, starting with Indonesia (92-96). The model describes multiple pathways through which malnutrition detrimentally affects cognitive development in children, namely through poor physical growth, motor development and activity, emotional regulation, caregiver behavior, and reduced exploration (91). Since then, others have built upon this model (21, 92). An adapted framework by Prado and Dewey (21) hypothesizes that improved nutrition can affect cognitive development directly through 1) brain development, by affecting brain metabolism, neurotransmitter function, and myelination, and indirectly through 2) the physical growth of a child, by improving muscle mass and linear growth, 3) the frequency and severity of sickness, by reducing susceptibility to infection and a reduced immune system, 4) a child's level of physical activity, by increasing muscle and bone strength, body proportions, and energy level, 5) interactions with caregivers, and 6) level of exploration of their environment.

Micronutrients are an important form of nutrition that can directly affect brain functions and structures, as described previously, but can also contribute to growth, activity, and reduced infection. Effects on growth and motor skills have been studied frequently, whereas effects on caregiver interactions less so. Importantly, few RCTs (97) studying the effects of a nutrition intervention on child development report mediating effects of variables such as growth, illness, and stimulation. The strength of these pathways are important to document and may explain some of the mixed effects seen in RCTs in LMICs.

2.4 Mediating pathways between nutrition and child development

Mediation through growth: The effect of nutrition on growth, in particular stunting, has been well documented with randomized trials. A meta-analysis of studies in children 6-24 months of age found that interventions providing nutrition counseling or complementary foods resulted in an additional weight gain of 0.25 kg and height gain of 0.54 cm (98). Another meta-analysis of iron, zinc, calcium, iodine, vitamin A, multiple micronutrients, protein, and food interventions on growth of children two years of age and older reported significant positive effects of zinc, vitamin A, multiple micronutrients, and protein on linear growth (99). The other half of the mediation pathway, from stunting to child development, has predominantly been examined using observational data, although several interventions aimed at improving stunting have also examined effects on child development (61, 87-89). In the 1990's Pollitt etal documented the association between physical growth and motor development in Indonesian children (100). They found that length-for-age, but not weight-for-length or weight-for-age, was significantly associated with gross motor development in children 6-18 months of age (100). Around the same time, Powell and Grantham-McGregor studied children under four years of age from poor neighborhoods in Jamaica and found that stunting and weight-for-age, but not wasting, were associated with mental development (101). Since then, much research has substantiated these results, so much so that stunting is now used as a proxy for poor development (1, 102). Recent work using the Early Childhood Development Index data collected from 2005 to 2015 in 3-4 year old children living in 35 LMICs showed that country-level socio-emotional and cognitive scores were significantly correlated with prevalence of stunting (r=0.72) (103). Thus, there is mounting evidence that stunting is associated with poor mental and motor development.

Mediation through illness: As for the mediating pathway through sickness, evidence suggests that malnutrition can have a significant effect on diarrhea duration (104, 105), severity, and mortality (106, 107). We also know that younger children who are frequently ill will spend more time close to their mother, foregoing exploring their environment and engaging with others. As a child ages and starts attending school, sickness leads to absence from school. Diarrheal disease is one of the leading causes of illness and death in LMICs (108). As with stunting, most of the evidence for the relation between diarrheal disease and child development is observational. For instance, in a longitudinal study in Brazilian urban slums, children's diarrheal disease was assessed in their first two years of life and children were followed up for cognitive testing 5-10 years later. Authors reported that diarrheal episodes were negatively correlated with children's IQ scores and verbal fluency (109, 110). A prospective cohort study of improved water and sanitation in infancy found that improved water and toilet access at 1 year was associated with higher language abilities at 5 and 8 years of age compared to children without access (111). However, other research has found that diarrhea and infection (other than malaria, trachoma and hookworm) does not have a strong impact on mental development (112, 113).

Mediation through motor development: Many have suggested that effects on cognitive development are mediated by motor development in young children (21, 91). Studies in Indonesia and Tanzania using cross-sectional and longitudinal data in structural equation models concluded that the associations between nutrition and mental development were mediated by motor activity and motor development (91, 96). Importantly, the benefits of motor development on mental development accrue only if they lead to richer experiences such as more objects to play with, varied places to explore and stimulating interactions with others (114, 115).This may

depend on the type of nutrition provided (116). For instance, Aburto et al found that child supplementation for 4 months with macro- and micronutrients enhanced their level of exploration (i.e., touching and manipulation of objects, fine motor abilities), whereas supplementation with only multiple micronutrients increased the level of activity performed (i.e., gross motor movements) (116).

Mediation through stimulation: Nutrition and dietary intake may also be associated with the level of psychosocial stimulation a child receives and relatedly, their cognitive development. Malnourished children may deprive themselves of stimulation by staying closer to their mothers and sitting on her lap more often than well-nourished children (117). They may also be seen as less mature and so elicit less stimulating verbal interaction and less varied meals than well-nourished children. Further, small and less vocal infants receive less care and stimulation from their mothers (118, 119). A study in Kenyan toddlers found that habitual dietary intake was positively associated with the provision of verbal and social interactions, and inversely associated with frequency of physical care, carrying, and holding (120). The level of stimulation provided to children can have significant effects on their physical and mental development. A meta-analysis of stimulation interventions on mental development in children under two years of age in LMICs indicated and effect size of 0.42 (95% CI 0.36, 0.48) for cognitive development and 0.47 (95% CI 0.37, 0.56) for language development (16). Further, in non-human primates, it has been shown that the deprivation of normal social interactions can elevate stress levels and lead to elevated glucocorticoids (121), with negative effects on hippocampal neurons and brain development on a cellular level (122).

In summary, evidence for pathways through linear growth are fairly strong, though pathways from nutrition through illness, motor development, and psychosocial stimulation are

less well studied. More evidence is needed to investigate the direct and indirect pathways through which nutrition can enhance the mental development of young children. Cross-sectional and longitudinal evidence is important, but RCTs of nutrition interventions need to also report these relationships when possible, so as to improve the design of interventions, monitor program achievements, but also more fully understand how to increase the potential impact nutrition can have on early child development.

2.5 Nutrition in the context of India

India is the second most populous country, with 1.3 billion people. According to the World Bank, it is ranked as a lower-middle income country. Prevalence of poverty and malnutrition in Bihar are some of the highest in the country. According to the latest National Family Health Survey (NFHS-4), only half of girls of school-going age have ever attended school, and fewer than half of females are literate. Just under two-thirds of households have electricity, one in four households use improved sanitation facilities, and fewer than 20% of households use clean fuel for cooking. Although malnutrition is improving, 48% of children under five years of age are stunted, 21% are wasted, and 44% are underweight. Further, one in every three children is anemic (hemoglobin < 11g/dL) (123).

Interestingly, over 90% of households use iodized salt, in part because of India's investment in food security (123). The Public Distribution System (PDS) is a food security scheme set up to help the population gain access to food at a subsidized rate. Salt (iodized), kerosene, wheat, rice, and sugar are available to card-carrying households at different rates and

quantities based on household size and income, with higher entitlements for those of lower income.

India also has a unique health infrastructure that utilizes two local community front-line health workers (FLWs), the Accredited Social Health Activists (ASHA) and the Anganwadi Workers (AWWs), to deliver products and messaging to women and children in all parts of the country. ASHAs are local women trained as health educators and are each responsible for an average of 150-200 households or a population of 1000. AWWs are part of the Integrated Child Development Services (ICDS) program in India. In addition to family planning and nutrition counseling and supplementation, they run preschool activities for children 3-5 years of age.

The PDS and the FLWs provide a unique delivery platform for nutrition products and fortified foods to the general population, and especially to those with the highest burden of malnutrition and those who would typically be difficult to reach. Evidence for the efficacy of several nutrition interventions is available; effectiveness trials using the established in-country avenues (i.e. PDS and FLWs) are needed. The Indian government is interested in piloting nutrition programs that utilize their existing social welfare infrastructure. For instance, the Food Safety and Standards Authority of India recently released new standards on fortification of food and the government has pledged to ensure that schemes such as the ICDS and PDS will be mandated to buy and distribute fortified foods. Many states are already fortifying edible oil and milk with vitamin A. Several states are also interested in starting distribution of double fortified salt through the PDS: Uttar Pradesh is currently running a pilot program in 10 districts; Madhya Pradesh and Tripura are initiating programs of their own. The Indian government's ongoing interest in health and nutrition provided us an opportunity to create the evidence base for scalable and effective solutions to reduce malnutrition.

2.7 Chapters 1 and 2 references

1. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, Lu C, McCoy DC, Fink G, Shawar YR, Shiffman J, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389(10064):77-90. doi: 10.1016/s0140-6736(16)31389-7.
2. Gertler P, Heckman J, Pinto R, Zanolini A, Vermeersch C, Walker S, Chang SM, Grantham-McGregor S. Labor market returns to an early childhood stimulation intervention in Jamaica. Science (New York, NY) 2014;344(6187):998-1001. doi: 10.1126/science.1251178.
3. Maluccio JA, Hoddinott J, Behrman JR, Martorell R, Quisumbing AR, Stein AD. The impact of improving nutrition during early childhood on education among Guatemalan adults. The Economic Journal 2009;119(537):734-63.
4. Walker SP, Chang SM, Vera-Hernandez M, Grantham-McGregor S. Early childhood stimulation benefits adult competence and reduces violent behavior. Pediatrics 2011;127(5):849-57. doi: 10.1542/peds.2010-2231.
5. Behrman JR, Calderon MC, Preston SH, Hoddinott J, Martorell R, Stein AD. Nutritional supplementation in girls influences the growth of their children: prospective study in Guatemala. The American journal of clinical nutrition 2009;90(5):1372-9. doi: 10.3945/ajcn.2009.27524.
6. Walker SP, Chang SM, Wright A, Osmond C, Grantham-McGregor SM. Early childhood stunting is associated with lower developmental levels in the subsequent generation of children. The Journal of nutrition 2015;145(4):823-8. doi: 10.3945/jn.114.200261.
7. Heckman JJ. The economics, technology, and neuroscience of human capability formation. Proceedings of the National Academy of Sciences of the United States of America 2007;104(33):13250-5. doi: 10.1073/pnas.0701362104.
8. Lien NM, Meyer KK, Winick M. Early malnutrition and "late" adoption: a study of their effects on the development of Korean orphans adopted into American families. The American journal of clinical nutrition 1977;30(10):1734-9.
9. Chugani HT, Behen ME, Muzik O, Juhasz C, Nagy F, Chugani DC. Local brain functional activity following early deprivation: a study of postinstitutionalized Romanian orphans. NeuroImage 2001;14(6):1290-301. doi: 10.1006/nimg.2001.0917.
10. MacLean K. The impact of institutionalization on child development. Development and psychopathology 2003;15(4):853-84.
11. Rutter M. Developmental catch-up, and deficit, following adoption after severe global early privation. English and Romanian Adoptees (ERA) Study Team. Journal of child psychology and psychiatry, and allied disciplines 1998;39(4):465-76.
12. Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M. Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 2006;117(6):2093-100. doi: 10.1542/peds.2005-1727.
13. Pollitt E. Developmental sequel from early nutritional deficiencies: conclusive and probability judgements. The Journal of nutrition 2000;130(2S Suppl):350s-3s.
14. Gottlieb G. Behavioral pathway to evolutionary change. Rivista di biologia 1991;84(3):385-409.

15. Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. Frontiers in human neuroscience 2009;3:31. doi: 10.3389/neuro.09.031.2009.
16. Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol 2015;66:433-57. doi: 10.1146/annurev-psych-010814-015128.
17. Habicht J-P, Martorell R. Objectives, research design, and implementation of the INCAP [Institute of Nutrition of Central America and Panama] longitudinal study. Food and Nutrition Bulletin (UNU) 1992.
18. Pollitt E, Gorman KS, Engle PL, Rivera JA, Martorell R. Nutrition in early life and the fulfillment of intellectual potential. The Journal of nutrition 1995;125(4 Suppl):1111s-8s.
19. Hoddinott J, Maluccio JA, Behrman JR, Flores R, Martorell R. Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults. Lancet 2008;371(9610):411-6. doi: 10.1016/s0140-6736(08)60205-6.
20. Kretchmer N, Beard JL, Carlson S. The role of nutrition in the development of normal cognition. The American journal of clinical nutrition 1996;63(6):997s-1001s.
21. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72(4):267-84. doi: 10.1111/nure.12102.
22. Petry N, Olofin I, Hurrell RF, Boy E, Wirth JP, Moursi M, Donahue Angel M, Rohner F. The Proportion of Anemia Associated with Iron Deficiency in Low, Medium, and High Human Development Index Countries: A Systematic Analysis of National Surveys. Nutrients 2016;8(11). doi: 10.3390/nu8110693.
23. Riggins T, Bauer PJ, Georgieff MK, Nelson CA. Declarative memory performance in infants of diabetic mothers. Advances in child development and behavior 2010;38:73-110.
24. Lozoff B, Georgieff MK. Iron deficiency and brain development. Seminars in pediatric neurology 2006;13(3):158-65. doi: 10.1016/j.spen.2006.08.004.
25. Haas JD, Brownlie Tt. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. The Journal of nutrition 2001;131(2s-2):676S-88S; discussion 88S-90S.
26. Ortiz E, Pasquini JM, Thompson K, Felt B, Butkus G, Beard J, Connor JR. Effect of manipulation of iron storage, transport, or availability on myelin composition and brain iron content in three different animal models. Journal of neuroscience research 2004;77(5):681-9. doi: 10.1002/jnr.20207.
27. Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK. Perinatal iron deficiency alters the neurochemical profile of the developing rat hippocampus. The Journal of nutrition 2003;133(10):3215-21.
28. Roncagliolo M, Benitez J, Eguibar JR. Progressive deterioration of central components of auditory brainstem responses during postnatal development of the myelin mutant taiep rat. Audiology & neuro-otology 2000;5(5):267-75. doi: 13891.
29. Roncagliolo M, Schlageter C, Leon C, Couve E, Bonansco C, Eguibar JR. Developmental impairment of compound action potential in the optic nerve of myelin mutant taiep rats. Brain research 2006;1067(1):78-84. doi: 10.1016/j.brainres.2005.10.010.
30. Madan N, Rusia U, Sikka M, Sharma S, Shankar N. Developmental and neurophysiologic deficits in iron deficiency in children. Indian journal of pediatrics 2011;78(1):58-64. doi: 10.1007/s12098-010-0192-0.

31. de los Monteros AE, Korsak RA, Tran T, Vu D, de Vellis J, Edmond J. Dietary iron and the integrity of the developing rat brain: a study with the artificially-reared rat pup. Cellular and molecular biology (Noisy-le-Grand, France) 2000;46(3):501-15.
32. Unger EL, Hurst AR, Georgieff MK, Schallert T, Rao R, Connor JR, Kaciroti N, Lozoff B, Felt B. Behavior and monoamine deficits in prenatal and perinatal iron deficiency are not corrected by early postnatal moderate-iron or high-iron diets in rats. The Journal of nutrition 2012;142(11):2040-9. doi: 10.3945/jn.112.162198.
33. Rao R, Tkac I, Schmidt AT, Georgieff MK. Fetal and neonatal iron deficiency causes volume loss and alters the neurochemical profile of the adult rat hippocampus. Nutritional neuroscience 2011;14(2):59-65. doi: 10.1179/1476830511y.0000000001.
34. Youdim MB, Ben-Shachar D, Yehuda S. Putative biological mechanisms of the effect of iron deficiency on brain biochemistry and behavior. The American journal of clinical nutrition 1989;50(3 Suppl):607-15; discussion 15-7.
35. Unger EL, Wiesinger JA, Hao L, Beard JL. Dopamine D2 receptor expression is altered by changes in cellular iron levels in PC12 cells and rat brain tissue. The Journal of nutrition 2008;138(12):2487-94. doi: 10.3945/jn.108.095224.
36. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64(5 Pt 2):S34-43; discussion S72-91.
37. Beard JL, Connor JR. Iron status and neural functioning. Annual review of nutrition 2003;23:41-58. doi: 10.1146/annurev.nutr.23.020102.075739.
38. Jorgenson LA, Wobken JD, Georgieff MK. Perinatal iron deficiency alters apical dendritic growth in hippocampal CA1 pyramidal neurons. Developmental neuroscience 2003;25(6):412-20. doi: 75667.
39. Beard JL, Felt B, Schallert T, Burhans M, Connor JR, Georgieff MK. Moderate iron deficiency in infancy: biology and behavior in young rats. Behavioural brain research 2006;170(2):224-32. doi: 10.1016/j.bbr.2006.02.024.
40. Shukla A, Agarwal KN, Chansuria JP, Taneja V. Effect of latent iron deficiency on 5-hydroxytryptamine metabolism in rat brain. Journal of neurochemistry 1989;52(3):730-5.
41. Felt BT, Lozoff B. Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early development. The Journal of nutrition 1996;126(3):693-701.
42. Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR, Georgieff MK, Lozoff B. Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. Behavioural brain research 2006;171(2):261-70. doi: 10.1016/j.bbr.2006.04.001.
43. Pinero D, Jones B, Beard J. Variations in dietary iron alter behavior in developing rats. The Journal of nutrition 2001;131(2):311-8.
44. McEchron MD, Cheng AY, Liu H, Connor JR, Gilmartin MR. Perinatal nutritional iron deficiency permanently impairs hippocampus-dependent trace fear conditioning in rats. Nutritional neuroscience 2005;8(3):195-206. doi: 10.1080/10284150500162952.
45. Dussault JH, Ruel J. Thyroid hormones and brain development. Annual review of physiology 1987;49:321-34. doi: 10.1146/annurev.ph.49.030187.001541.
46. de Escobar GM, Obregon MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. Public health nutrition 2007;10(12a):1554-70. doi: 10.1017/s1368980007360928.

47. Liu JL, Zhuang ZJ, Tan YB, Shi ZF, Li XT, Yang XB, Wu JB, Chen BZ, Zhang JX, Qin JX, et al. Morphologic study on cerebral cortex development in therapeutically aborted fetuses in an endemic goiter region in Guizhou. Chinese medical journal 1984;97(1):67-72.
48. Bougma K, Aboud FE, Harding KB, Marquis GS. Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis. Nutrients 2013;5(4):1384-416. doi: 10.3390/nu5041384.
49. McNall AD, Etherton TD, Fosmire GJ. The impaired growth induced by zinc deficiency in rats is associated with decreased expression of the hepatic insulin-like growth factor I and growth hormone receptor genes. The Journal of nutrition 1995;125(4):874-9.
50. Terhune MW, Sandstead HH. Decreased RNA polymerase activity in mammalian zinc deficiency. Science (New York, NY) 1972;177(4043):68-9.
51. Duncan JR, Hurley LS. Thymidine kinase and DNA polymerase activity in normal and zinc deficient developing rat embryos. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine (New York, NY) 1978;159(1):39-43.
52. Walsh CT, Sandstead HH, Prasad AS, Newberne PM, Fraker PJ. Zinc: health effects and research priorities for the 1990s. Environmental health perspectives 1994;102 Suppl 2:5-46.
53. Hicks SE, Wallwork JC. Effect of dietary zinc deficiency on protein synthesis in cell-free systems isolated from rat liver. The Journal of nutrition 1987;117(7):1234-40.
54. Fuglestad AJ, Rao R, Georgieff MK, Code MM. The role of nutrition in cognitive development. Handbook of developmental cognitive neuroscience 2008:623-41.
55. Dvergsten CL, Fosmire GJ, Ollerich DA, Sandstead HH. Alterations in the postnatal development of the cerebellar cortex due to zinc deficiency. I. Impaired acquisition of granule cells. Brain research 1983;271(2):217-26.
56. Frederickson CJ, Danscher G. Zinc-containing neurons in hippocampus and related CNS structures. Progress in brain research 1990;83:71-84.
57. Dvergsten CL, Fosmire GJ, Ollerich DA, Sandstead HH. Alterations in the postnatal development of the cerebellar cortex due to zinc deficiency. II. Impaired maturation of Purkinje cells. Brain research 1984;318(1):11-20.
58. Hesse GW. Chronic zinc deficiency alters neuronal function of hippocampal mossy fibers. Science (New York, NY) 1979;205(4410):1005-7.
59. Celentano JJ, Gyenes M, Gibbs TT, Farb DH. Negative modulation of the gamma-aminobutyric acid response by extracellular zinc. Molecular pharmacology 1991;40(5):766-73.
60. Westbrook GL, Mayer ML. Micromolar concentrations of Zn2+ antagonize NMDA and GABA responses of hippocampal neurons. Nature 1987;328(6131):640-3. doi: 10.1038/328640a0.
61. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children under-two in low- and middle-income countries. Maternal & child nutrition 2017;13(1). doi: 10.1111/mcn.12229.
62. Black MM, Sazawal S, Black RE, Khosla S, Kumar J, Menon V. Cognitive and motor development among small-for-gestational-age infants: impact of zinc supplementation, birth weight, and caregiving practices. Pediatrics 2004;113(5):1297-305.

63. Molloy AM, Kirke PN, Troendle JF, Burke H, Sutton M, Brody LC, Scott JM, Mills JL. Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic Acid fortification. Pediatrics 2009;123(3):917-23. doi: 10.1542/peds.2008-1173.
64. Guilarte TR. Vitamin B6 and cognitive development: recent research findings from human and animal studies. Nutr Rev 1993;51(7):193-8.
65. Chang SJ, Kirksey A, Morre DM. Effects of vitamin B-6 deficiency on morphological changes in dendritic trees of Purkinje cells in developing cerebellum of rats. The Journal of nutrition 1981;111(5):848-57.
66. Groziak SM, Kirksey A. Effects of maternal restriction in vitamin B-6 on neocortex development in rats: neuron differentiation and synaptogenesis. The Journal of nutrition 1990;120(5):485-92.
67. Guilarte TR, Wagner HN, Jr., Frost JJ. Effects of perinatal vitamin B6 deficiency on dopaminergic neurochemistry. Journal of neurochemistry 1987;48(2):432-9.
68. Morre DM, Kirksey A, Das GD. Effects of vitamin B-6 deficiency on the developing central nervous system of the rat. Myelination. The Journal of nutrition 1978;108(8):1260-5.
69. Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain research 2008;1237:35-43. doi: 10.1016/j.brainres.2008.08.078.
70. Innis SM. Dietary (n-3) fatty acids and brain development. The Journal of nutrition 2007;137(4):855-9.
71. Karr JE, Alexander JE, Winningham RG. Omega-3 polyunsaturated fatty acids and cognition throughout the lifespan: a review. Nutritional neuroscience 2011;14(5):216-25. doi: 10.1179/1476830511y.0000000012.
72. Colombo J, Jill Shaddy D, Kerling EH, Gustafson KM, Carlson SE. Docosahexaenoic acid (DHA) and arachidonic acid (ARA) balance in developmental outcomes. Prostaglandins, leukotrienes, and essential fatty acids 2017;121:52-6. doi: 10.1016/j.plefa.2017.05.005.
73. Szajewska H, Ruszczynski M, Chmielewska A. Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials. The American journal of clinical nutrition 2010;91(6):1684-90. doi: 10.3945/ajcn.2010.29191.
74. Eilander A, Gera T, Sachdev HS, Transler C, van der Knaap HC, Kok FJ, Osendarp SJ. Multiple micronutrient supplementation for improving cognitive performance in children: systematic review of randomized controlled trials. The American journal of clinical nutrition 2010;91(1):115-30. doi: 10.3945/ajcn.2009.28376.
75. Ramakrishnan U, Goldenberg T, Allen LH. Do multiple micronutrient interventions improve child health, growth, and development? The Journal of nutrition 2011;141(11):2066-75. doi: 10.3945/jn.111.146845.
76. Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. The Lancet 2014.
77. Yousafzai AK, Obradovic J, Rasheed MA, Rizvi A, Portilla XA, Tirado-Strayer N, Siyal S, Memon U. 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. The Lancet Global health 2016;4(8):e548-58. doi: 10.1016/s2214-109x(16)30100-0.
78. Pasricha S-R, Hayes E, Kalumba K, Biggs B-A. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. The Lancet Global Health 2013;1(2):e77-e86.
79. Thompson J, Biggs BA, Pasricha SR. Effects of daily iron supplementation in 2- to 5-year-old children: systematic review and meta-analysis. Pediatrics 2013;131(4):739-53. doi: 10.1542/peds.2012-2256.
80. Deinard AS, List A, Lindgren B, Hunt JV, Chang PN. Cognitive deficits in iron-deficient and iron-deficient anemic children. The Journal of pediatrics 1986;108(5 Pt 1):681-9.
81. Stoltzfus RJ, Kvalsvig JD, Chwaya HM, Montresor A, Albonico M, Tielsch JM, Savioli L, Pollitt E. Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. Bmj 2001;323(7326):1389-93.
82. Akman M, Cebeci D, Okur V, Angin H, Abali O, Akman AC. The effects of iron deficiency on infants' developmental test performance. Acta paediatrica (Oslo, Norway : 1992) 2004;93(10):1391-6.
83. Friel JK, Aziz K, Andrews WL, Harding SV, Courage ML, Adams RJ. A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. The Journal of pediatrics 2003;143(5):582-6. doi: 10.1067/s0022-3476(03)00301-9.
84. Oski FA, Honig AS. The effects of therapy on the developmental scores of iron-deficient infants. The Journal of pediatrics 1978;92(1):21-5.
85. Chen CM, Wang YY, Chang SY. Effect of in-home fortification of complementary feeding on intellectual development of Chinese children. Biomedical and environmental sciences : BES 2010;23(2):83-91. doi: 10.1016/s0895-3988(10)60036-0.
86. Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003;112(4):846-54.
87. Prado EL, Abbeddou S, Yakes Jimenez E, Some JW, Ouedraogo ZP, Vosti SA, Dewey KG, Brown KH, Hess SY, Ouedraogo JB. Lipid-Based Nutrient Supplements Plus Malaria and Diarrhea Treatment Increase Infant Development Scores in a Cluster-Randomized Trial in Burkina Faso. The Journal of nutrition 2016. doi: 10.3945/jn.115.225524.
88. Prado EL, Maleta K, Ashorn P, Ashorn U, Vosti SA, Sadalaki J, Dewey KG. Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi. The American journal of clinical nutrition 2016;103(3):784-93. doi: 10.3945/ajcn.115.114579.
89. Prado EL, Adu-Afarwuah S, Lartey A, Ocansey M, Ashorn P, Vosti SA, Dewey KG. Effects of pre- and post-natal lipid-based nutrient supplements on infant development in a randomized trial in Ghana. Early human development 2016;99:43-51. doi: 10.1016/j.earlhumdev.2016.05.011.
90. Matias SL, Mridha MK, Tofail F, Arnold CD, Khan MS, Siddiqui Z, Ullah MB, Dewey KG. Home fortification during the first 1000 d improves child development in

Bangladesh: a cluster-randomized effectiveness trial. The American journal of clinical nutrition 2017. doi: 10.3945/ajcn.116.150318.
91. Pollitt E. A developmental view of the undernourished child: background and purpose of the study in Pangalengan, Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S2-10.
92. Olney DK, Kariger PK, Stoltzfus RJ, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Pollitt E. Development of nutritionally at-risk young children is predicted by malaria, anemia, and stunting in Pemba, Zanzibar. The Journal of nutrition 2009;139(4):763-72. doi: 10.3945/jn.107.086231.
93. Pollitt E, Jahari A, Walka H. A developmental view of the effects of an energy and micronutrient supplement in undernourished children in Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S107-13.
94. Walka H, Pollitt E. A preliminary test of a developmental model for the study of undernourished children in Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S21-7.
95. Prado EL, Abbeddou S, Adu-Afarwuah S, Arimond M, Ashorn P, Ashorn U, Bendabenda J, Brown KH, Hess SY, Kortekangas E, et al. Predictors and pathways of language and motor development in four prospective cohorts of young children in Ghana, Malawi, and Burkina Faso. Journal of child psychology and psychiatry, and allied disciplines 2017. doi: 10.1111/jcpp.12751.
96. Olney DK, Kariger PK, Stoltzfus RJ, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Pollitt E. Developmental effects of micronutrient supplementation and malaria in Zanzibari children. Early human development 2013;89(9):667-74. doi: 10.1016/j.earlhumdev.2013.04.013.
97. Frongillo EA, Nguyen PH, Saha KK, Sanghvi T, Afsana K, Haque R, Baker J, Ruel MT, Rawat R, Menon P. Large-Scale Behavior-Change Initiative for Infant and Young Child Feeding Advanced Language and Motor Development in a Cluster-Randomized Program Evaluation in Bangladesh. The Journal of nutrition 2017;147(2):256-63. doi: 10.3945/jn.116.240861.
98. Imdad A, Yakoob MY, Bhutta ZA. Impact of maternal education about complementary feeding and provision of complementary foods on child growth in developing countries. BMC public health 2011;11 Suppl 3:S25. doi: 10.1186/1471-2458-11-s3-s25.
99. Roberts JL, Stein AD. The Impact of Nutritional Interventions beyond the First 2 Years of Life on Linear Growth: A Systematic Review and Meta-Analysis. Advances in nutrition (Bethesda, Md) 2017;8(2):323-36. doi: 10.3945/an.116.013938.
100. Pollitt E, Husaini MA, Harahap H, Halati S, Nugraheni A, Sherlock AO. Stunting and delayed motor development in rural West Java. American Journal of Human Biology 1994;6(5):627-35.
101. Powell CA, Grantham-McGregor S. The ecology of nutritional status and development in young children in Kingston, Jamaica. The American journal of clinical nutrition 1985;41(6):1322-31.
102. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369(9555):60-70. doi: 10.1016/s0140-6736(07)60032-4.
103. McCoy DC, Peet ED, Ezzati M, Danaei G, Black MM, Sudfeld CR, Fawzi W, Fink G. Early Childhood Developmental Status in Low- and Middle-Income Countries: National,

Regional, and Global Prevalence Estimates Using Predictive Modeling. PLoS medicine 2016;13(6):e1002034. doi: 10.1371/journal.pmed.1002034.
104. Black RE, Brown KH, Becker S. Malnutrition is a determining factor in diarrheal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. The American journal of clinical nutrition 1984;39(1):87-94.
105. Guerrant RL, Schorling JB, McAuliffe JF, de Souza MA. Diarrhea as a cause and an effect of malnutrition: diarrhea prevents catch-up growth and malnutrition increases diarrhea frequency and duration. The American journal of tropical medicine and hygiene 1992;47(1 Pt 2):28-35.
106. Mathur R, Reddy V, Naidu AN, Ravikumar, Krishnamachari KA. Nutritional status and diarrhoeal morbidity: a longitudinal study in rural Indian preschool children. Human nutrition Clinical nutrition 1985;39(6):447-54.
107. Ryder RW, Reeves WC, Sack RB. Risk factors for fatal childhood diarrhea: a case-control study from two remote Panamanian islands. American journal of epidemiology 1985;121(4):605-10.
108. Santosham M, Chandran A, Fitzwater S, Fischer-Walker C, Baqui AH, Black R. Progress and barriers for the control of diarrhoeal disease. Lancet 2010;376(9734):63-7. doi: 10.1016/s0140-6736(10)60356-x.
109. Patrick PD, Oria RB, Madhavan V, Pinkerton RC, Lorntz B, Lima AA, Guerrant RL. Limitations in verbal fluency following heavy burdens of early childhood diarrhea in Brazilian shantytown children. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence 2005;11(3):233-44. doi: 10.1080/092970490911252.
110. Niehaus MD, Moore SR, Patrick PD, Derr LL, Lorntz B, Lima AA, Guerrant RL. Early childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. The American journal of tropical medicine and hygiene 2002;66(5):590-3.
111. Dearden KA, Brennan AT, Behrman JR, Schott W, Crookston BT, Humphries DL, Penny ME, Fernald LC. Does household access to improved water and sanitation in infancy and childhood predict better vocabulary test performance in Ethiopian, Indian, Peruvian and Vietnamese cohort studies? BMJ open 2017;7(3):e013201. doi: 10.1136/bmjopen-2016-013201.
112. Fischer Walker CL, Lamberti L, Adair L, Guerrant RL, Lescano AG, Martorell R, Pinkerton RC, Black RE. Does childhood diarrhea influence cognition beyond the diarrhea-stunting pathway? PLoS One 2012;7(10):e47908. doi: 10.1371/journal.pone.0047908.
113. Taylor-Robinson DC, Jones AP, Garner P. Deworming drugs for treating soil-transmitted intestinal worms in children: effects on growth and school performance. The Cochrane database of systematic reviews 2007(4):Cd000371. doi: 10.1002/14651858.CD000371.pub3.
114. Adolph KE, Tamis-LeMonda CS. The Costs and Benefits of Development: The Transition From Crawling to Walking. Child Dev Perspect 2014;8(4):187-92. doi: 10.1111/cdep.12085.
115. Tamis-LeMonda CS, Bornstein MH, Baumwell L. Maternal responsiveness and children's achievement of language milestones. Child development 2001;72(3):748-67.

116. Aburto NJ, Ramirez-Zea M, Neufeld LM, Flores-Ayala R. The effect of nutritional supplementation on physical activity and exploratory behavior of Mexican infants aged 8-12 months. European journal of clinical nutrition 2010;64(6):644-51. doi: 10.1038/ejcn.2010.52.
117. Graves P. Nutrition and infant behavior: a replication study in the Katmandu Valley, Nepal. The American journal of clinical nutrition 1978;31(3):541-51.
118. Rahmanifar A, Kirksey A, Wachs TD, McCabe GP, Bishry Z, Galal OM, Harrison GG, Jerome NW. Diet during lactation associated with infant behavior and caregiver-infant interaction in a semirural Egyptian village. The Journal of nutrition 1993;123(2):164-75.
119. Aboud FE, Alemu T. Nutrition, maternal responsiveness and mental development of Ethiopian children. Social science & medicine (1982) 1995;41(5):725-32.
120. Sigman M, Neumann C, Baksh M, Bwibo N, McDonald MA. Relationship between nutrition and development in Kenyan toddlers. The Journal of pediatrics 1989;115(3):357-64.
121. Higley JD, Suomi SJ, Linnoila M. A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. Biological psychiatry 1992;32(2):127-45.
122. Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. Proceedings of the National Academy of Sciences of the United States of America 1998;95(9):5335-40.
123. International Institute of Population Sciences. National Family Health Survey (NFHS-4), 2015-2016: India. 2016.

Chapter 3: A Meta-analysis of Nutrition Interventions on Mental Development of Children Under-Two in Low- and Middle-Income Countries

Leila Margaret Larson[1], Aisha K Yousafzai[2]

[1]Emory University, Nutrition and Health Sciences Program, Laney Graduate School, 1462 Clifton Rd, Suite 314, Atlanta, Georgia, 30322

[2]Aga Khan University, Department of Paediatrics and Child Health, Division of Women and Child Health, Stadium Road PO Box 3500, Karachi 74800, Sindh, Pakistan

From Maternal and Child Nutrition, Vol. 13, Issue 1, January 2017

Published online ahead of print November 2015

3.1 Abstract

Interventions to improve nutritional status of young children in low- and middle-income countries (LMIC) may have the added benefit of improving their mental and motor development. This meta-analysis updates and goes beyond previous ones by answering two important questions: 1) do prenatal and postnatal nutritional inputs improve mental development, and 2) are effects on mental development associated with two theoretically interesting mediators namely physical growth and motor development? The meta-analysis of articles on Medline, PsycINFO, Global Health and Embase was limited to randomized trials in LMICs, with mental development of children from birth to age two years as an outcome. The initial yield of 2689 studies was reduced to 33; 12 received a global quality rating of strong. Of the 10 prenatal and 23 postnatal nutrition interventions, the majority used zinc, iron/folic acid, vitamin A or multiple micronutrients, with a few evaluating macronutrients. The weighted mean effect size, Cohen's *d* (95% CI) for prenatal and postnatal nutrition interventions on mental development was 0.04 (-0.01, 0.092) and 0.08 (0.02, 0.13), respectively. Postnatal supplements consisting of macronutrients yielded an effect size *d* (95% CI) of 0.14 (0.01, 0.27), multiple micronutrients 0.08 (-0.01, 0.18) and single micronutrients 0.06 (-0.002, 0.12). Motor development, but not growth status, effect sizes were significantly associated with mental development in postnatal interventions. In summary, nutrition interventions had small effects on mental development. Future studies might have greater effect if they addressed macronutrient deficiencies combined with child stimulation and hygiene and sanitation interventions.

3.2 Introduction

Malnourished children consistently perform poorly on tests of mental development in both cross-sectional and longitudinal studies (1). The impact of nutrition on cognitive and language development is particularly important in low- and middle-income countries (LMIC) where many children are affected by both macronutrient and micronutrient deficiencies. Consequently, a number of recent nutrition interventions have examined cognitive benefits along with physical growth. The first objective of this review is to examine accumulating evidence for the effects of both macro and micronutrient supplements on mental development in young children less than two years of age.

The secondary aim is to examine the proposed pathways by which nutrition may impact mental development. It is critical to examine mediators in the pathways showing how nutritional status/physical growth leads to mental development. Previous meta-analyses have not examined these mediators. Postnatally, better nutrition may influence mental development through several pathways. In addition to direct effects on brain development, another is through motor development: children with better nutrition may walk at an earlier age (2), leading to increased interaction with, and exploration of, their environment. Adolph and Tamis-LeMonda argue that infants willingly abandon their status as expert crawlers to become unsteady walkers, in part because it leads to richer experiences, more ground to cover and objects to play with, and a different type of interaction with others (3). Height and weight may also influence the caregiver's behavior toward the child, such as providing more sophisticated stimulation to a child who appears more mature physically and less to a malnourished child (4). Both pathways enhance stimulation and may in turn affect children's overall cognitive performance (5). This review examines mental development and motor development outcomes of children under-24 months receiving a nutrition intervention. It also investigates whether children's mental development (mainly cognitive) is associated with greater growth and motor development, thus supporting explanations of the link between nutrition and mental development.

Two previous systematic reviews examined the effects of multiple micronutrients on cognitive outcomes in children, together including only two randomized controlled trials (RCT) of children under-two years (6, 7). Several studies assessed motor development only. Eilander et al (2010) included one study on mental development with no significant effects (8). Two other trials included outcomes of motor development, specifically the age of walking unassisted, where multiple micronutrients had significantly positive effects (9, 10). In Ramakrishnan et al's review (7) only one study, different than the one noted by Eilander and colleagues, looked at mental development and found no significant effects due to multiple micronutrients (11). These reviews were limited to postnatal micronutrient interventions only with few assessing child cognition outcomes; therefore, the effect of micronutrient supplementation on children's cognition as well as the comparison with macronutrient supplementation requires further investigation.

A third systematic review examined the effects of a single micronutrient, namely iron supplements, in seven RCTs where there was a non-significant effect on mental and motor development of children under-24 months of age (12). The effect of iron, a single micronutrient, compared with multiple micronutrient supplementation can be further analyzed. Finally, a fourth systematic review found a small effect of postnatal nutrition interventions on mental development but was confined to studies between 2000 and 2012, and so excluded many studies conducted before that date when macronutrients were more likely to be studied (13). Further, this review did not examine possible explanations for the small overall effect seen.

A systematic review looking at prenatal micronutrient supplementation and its effect on children's mental development found no significant results (14). However, psychomotor outcomes improved in two studies using multiple micronutrients and one study using fish oil (15-17). Several other fatty acid reviews have been conducted and found non-significant overall effects on mental and

motor development (18-22), but their findings are largely from RCTs in high-income countries limiting the interpretation of these data for LMICs where maternal malnutrition is highly prevalent.

In recent years, the number of nutrition intervention studies assessing development as a primary or secondary outcome has increased making it timely for current review. The primary objective of this meta-analysis is to examine the effect of nutrition supplementation on mental development in LMICs. This meta-analysis extends upon previous systematic reviews by addressing effects of pre and postnatal interventions, as well as micro and macronutrition supplementation and their effects on mental development. The secondary objective is to examine the potential pathways by which nutritional inputs may affect mental development, namely nutritional status and motor development. Motor development has been used to explain how nutritional inputs affect mental development (4, 5); for example, by enhancing activity and exploration with length and weight underpinning this explanation. We examine these associations in order to identify key mediators, but also potential barriers to why mental development may not be affected. This review is limited to RCTs in LMICs to study the effect of nutrition in resource-poor settings and is also limited to children under the age of two years. The first 1000 days is now of greatest concern to nutritionists and is an age of rapid brain development (23). As a result, improved conditions before the age of two years may have greater benefits on mental and motor development than at a later age. Therefore, this review looks at the effect of nutrition interventions in pregnant and lactating mothers on their children's mental development before the age of two years, and also the effect of nutrition interventions in children on their mental development until the age of two years.

3.3 Methods

3.3.1 Study search

A search of four databases, Global Health, Medline, PsycINFO, and Embase was conducted to identify articles on nutrition interventions and mental development. The search strategy included topics related to nutrition, mental development, and evaluated interventions, using the following terms: nutrient requirements; infant foods; feeding behavior; food supplements; nutrients; micronutrient, diet; iodine; iron; stunting; height; malnutrition; Bayley; PPVT; language; cognitive; trial; intervention; program; RCT. The search was limited to years January 1970 to September 2014, and to English language publications. In Medline, it was possible to limit the age from birth to 24 months. The references from the identified articles were also searched for any additional studies. The PRISMA guidelines were followed (24). The clinical trials registry (www.clinicaltrials.gov) was searched for relevant trials in the same study period that were not captured in the peer reviewed literature search. However, no additional trials were found.

3.3.2 Inclusion and exclusion criteria

Inclusion criteria were listed as: LMIC; RCT; mental development outcome measured in children from birth to 24 months; and an empirical analysis of the data. Fine and gross motor, morbidity, mortality, growth and other nutritional outcomes were recorded if they were analyzed in the article. Authors were contacted to obtain outcome statistics if they were not included in the published article. Both prenatal and postnatal nutritional supplementation trials were included. Samples of preterm children were excluded because the degree of prematurity cannot be reliably assessed in many LMICs, particularly with home births. Studies with supplementation periods shorter than two months were excluded. Other exclusion criteria included: no specific child- or prenatal-based intervention, such as screening or cash transfer interventions; hospital-based studies for children with a major disease or

disorder, such as cancer or diabetes; autistic children; and reviews or secondary analyses of studies that were already included.

3.3.3 Study selection and data extraction

A first pass of the articles yielded by the search strategy examined the country of data, age of children, and nature of the sample. This yielded still a large number of citations, which were further examined in a second pass that considered all inclusion criteria. These two passes were done independently by two reviewers. Data extraction was also completed independently by these two reviewers. Discrepancies were resolved through discussion. Data extraction tables were created with the following information: 1) reference and country; 2) sample size analyzed, ages at baseline and endpoint, baseline height-for-age z-score (HAZ) or body mass index (BMI); 3) study design; 4) intervention including nutrients, duration; 5) main mental development outcomes, nutritional outcomes, motor outcomes, and effect size Cohen's *d*; and 6) quality assessment. The effect size was the main summary measure. All mental development test scores were retrieved, whether they included separate or combined cognitive and language subtest scores. Most studies had groups that were comparable at baseline on variables that correlated with the outcome. For this reason, the outcome mean and standard deviation at the study endpoint was used to calculate the effect size for each comparison. Effect sizes were calculated for all group comparisons in a single study.

3.3.4 Quality assessment of RCTs

The Effective Public Health Practice Project (EPHPP) quality assessment tool was used to assign a global rating to each study (25). Quality is rated according to selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and

analysis. Ratings of prenatal and postnatal studies were assigned by two independent reviewers to ensure reliability (kappa=0.69 for prenatal studies and kappa=0.72 for postnatal studies). We used funnel plots to assess potential publication bias.

3.3.5 Analysis

The effect size Cohen's *d* for each group comparison was calculated by dividing the difference in the mean endpoint scores for the intervention and control group by the pooled standard deviation. These effect sizes were then weighted by the inverse variance of the endpoint scores. The overall effect size was calculated by taking the mean of these weighted individual trial effect sizes. In order to appropriately assess for statistical heterogeneity among trials, we ran a chi squared test on the Cochrane's heterogeneity statistic Q, and calculated the I^2 statistic (calculated as $I^2 = (Q-df)/Q$, where df is the degree of freedom). For prenatal trials, the Q-statistic was 15.46 with a p-value of 0.22 and I^2 of 22.39; postnatal trials resulted in a Q-statistic of 41.39 with a p-value of 0.08 and I^2 of 25.11. These I^2 values represent moderate heterogeneity and therefore random effects models were used. The statistical software SAS version 9.4 was used for the analysis.

Specific to our secondary objective, we used PROC MIXED to run a random effects meta-regression model to examine whether study quality (its global rating), intervention type, sample size, baseline HAZ (for postnatal studies) or baseline maternal BMI (for prenatal studies), motor development effect size, and endline HAZ effect size were significantly associated with mental development effect size. The study was included in the model as a random effect and study quality, intervention type, sample size, baseline HAZ or BMI, motor development effect size, and endline HAZ effect size were used as fixed effects in the model. We used the empirical sandwich estimator to account for covariance correlation matrix between and within studies. This analysis adjusts for

correlations among multiple effects derived from the different interventions provided within specific studies.

3.4 Results

3.4.1 Search flow

The original search of all four databases yielded 2689 citations with 936 excluded due to duplicates. The first pass reduced the number of studies to 188, and the second pass left 33 RCTs of nutrition interventions analyzing mental development in children aged less than two years in LMICs (**Figure 3.1**). An additional 12 studies were identified from recent reviews that appeared in the database search, of which none was included in the final sample after full text review.

3.4.2 Study characteristics

The studies included in the current meta-analysis were classified into two main categories (see **Tables 3.1 and 3.2**): 1) those where nutrition was given prenatally and children under the age of two were followed-up after birth to test mental development; and 2) those where supplementation or some other type of nutrition intervention was given to children under the age of two years and their mental development was assessed shortly after. Ten studies fit the former category and 23 met the latter category. All but one had samples that ranged from well-nourished to moderately malnourished on average. Prenatal interventions included 5352 children; postnatal intervention included 6485 children.

Most studies were conducted in low-income countries from Africa and South Asia. Some were conducted in Latin America, where countries have higher Human Development Indexes; nonetheless samples included malnourished children from urban slums or rural sites.

The prenatal studies used supplementation in the second and/or third trimesters of pregnancy. Most of the postnatal nutrition interventions started when the child was six months of age. However, six trials began within the first two months after birth. The duration of the interventions ranged from two months to 24 months, with a mode of six months.

The majority of studies used zinc, iron/folic acid, vitamin A, iodine, or multiple micronutrients (n=24). Others looked at the effect of supplementation with fatty acids or food supplements (n=8), and one gave a calorie- and protein-dense milk supplement. With respect to the comparison group, the majority of studies provided a placebo or nothing (n=19), and the remainder provided either fewer micronutrients or lower energy supplements.

3.4.3 Mental development tests used

Almost all of the studies included in this meta-analysis used a direct assessment of the child, where a sequence of tasks, ordered in terms of level of difficulty, is given to the child and scored as pass or fail. Items involve measuring competencies related to cognition, expressive and receptive language, and fine motor skills.

Twenty-four studies used the Bayley Scales of Infant Development (BSID-I, -II, or -III)–Mental Scale (26). Four studies instead administered the Griffiths Mental Developmental Scale (27), while single studies used the Fagan Test of Infant Intelligence (28), a language test derived from BSID II, language milestones, or a two-item problem-solving test included in the BSID II. Most studies were unable to separate language and cognition subscores and so the effect of the intervention on these distinct outcomes is not clear. When language and cognition were measured separately, cognition was used to calculate the effect size for mental development. The Bayley, Griffith, and milestones were used to measure gross motor development if included as an outcome in the study.

3.4.4 Effects of nutrition interventions on mental development

Regarding prenatal supplementation interventions, the mean effect size for mental development was very small and non-significant at $d = 0.04$ (95% CI: -0.01, 0.09) (n=10 studies, 5352 participants), ranging from -0.31 to 0.57. The forest plot for mental scores from prenatal supplementation interventions is shown in **Figure 3.2**. Most of the interventions had very little positive effect on mental development, and some even had significant negative effects. However, the 10 studies in this group were quite heterogeneous with respect to intervention, preventing analysis of trends among similar studies.

Looking next at postnatal trials, nutrition interventions resulted in a significant mean effect size Cohen's *d* for mental development of $d = 0.08$ (95% CI: 0.02, 0.13) (n=23 studies, 6485 participants) with a range from -0.33 to 1.02. The forest plot for mental development scores from postnatal supplementation trials is shown in **Figure 3.3**. Excluding the outlier, the study by Idjradinata and Pollitt (29), the effect size remained similar at $d = 0.07$ (95% CI: 0.02, 0.12) (n=22 studies, 6441 participants).

Positive outcomes on mental development in postnatal interventions are seen with the use of calorie- and protein-dense milk, gangliosides added to milk, and the use of fortified porridge or a rice and lentil mixture (30-34). Multiple micronutrients, iron and folic acid, and zinc interventions showed mixed results. Multiple micronutrient supplementation of children seems to have a slightly higher positive effect on mental development when compared to supplementation with only one micronutrient. When stratified by supplementation type, the weighted effect sizes for multiple micronutrient interventions (**Figure 3.4**) and for single micronutrient interventions (**Figure 3.5**) are $d = 0.08$ (95% CI: -0.01, 0.18) (n=6 interventions, 1915 participants) and $d = 0.06$ (95% CI: -0.002, 0.12) (n=19 interventions, 3803 participants), respectively.

There could be some added benefit from the provision of fats, energy and protein. When stratifying the analysis by interventions with energy, fat or protein compared to those giving one or more micronutrients, we see a slightly higher benefit from the former. The weighted effect size for interventions giving energy, fat, omega-3 fatty acid, or protein (**Figure 3.6**) is d = 0.14 (95% CI: 0.01, 0.27) (n=7 interventions, 893 participants) and for interventions giving one or multiple micronutrients, it is d = 0.07 (95% CI: 0.02, 0.12) (n=25 interventions, 5592 participants).

The funnel plot for postnatal interventions looks symmetrical (**Figure 3.7**). Consequently, we ruled out bias in publishing only studies with significant effects. Publication bias seems to be more of an issue with prenatal supplementation interventions. The funnel plot shown in **Figure 3.8** is asymmetrical, with more studies with positive effect sizes. It should be noted that there are fewer prenatal supplementation trials compared to postnatal supplementation trials.

Using the random effects meta-regression on mental development, we found that quality of the study, sample size, and intervention type (micronutrient or energy given) were not significant predictors of either postnatal or prenatal effect size. Further, baseline HAZ (n=19 interventions) was not a significant predictor of postnatal effect size and baseline maternal BMI (n=10 interventions) was not a significant predictor of prenatal effect size. A random effects model was fit to look at the association between motor and mental development and found that motor development effect size (n=11 prenatal interventions, n=22 postnatal interventions) was significantly associated with mental development effect size (regression coefficient=0.32, 95% CI: 0.09, 0.54) in postnatal but not prenatal interventions. End-line HAZ effect size (n=19 postnatal interventions), however, was not significantly associated with mental development.

3.5 Discussion

Taken together, nutrition interventions did not seem to have a significant effect on mental (cognitive) development of children under-two years in LMICs. The effect sizes were d=0.04 for prenatal nutrition and d=0.08 for postnatal nutrition. This meta-analysis comparing interventions between studies, although not statistically significant, showed a trend toward more benefit on cognitive development from the provision of postnatal multiple micronutrients compared to a single micronutrient, and also for provision of fats, energy and protein with micronutrients compared to micronutrients alone. This suggests that the most promising approach is a combination of macro- and micronutrients; however, future work would need to examine these approaches further to determine significant benefits of combined macro and micronutrient supplementation with single approaches.

Several lines of evidence support the need for both macro and micronutrients in brain development and particularly in LMICs samples. For example, during infancy 20% of the body's energy is used to support brain structure and function (35). Furthermore, specific macro- and micronutrients gain added importance when considering how widespread is their presence in the brain is. Fats have important functions in synaptogenesis, membrane function and the synthesis of myelin that coats neurons and is thought to speed processing (36). Iron plays a role in myelination, transmitter synthesis and hippocampal energy metabolism in the neonatal period (36). However, the relation between brain and behavior is not always straightforward; a lack of correspondence may occur if secondary sites of the brain compensate for deficits in the primary site. For example, visual sites of the brain may compensate for deficits in the more efficient language sites for reading (37). The trend toward a larger impact of fats, calories and protein could be a function of the setting of these studies, all being in food insecure areas where both macro and micronutrients are lacking in diets. There is a need to explore the effect of fat, energy and protein provision in addition to micronutrients on cognitive outcomes of children in resource poor areas.

The effect sizes of motor development are significantly associated with those of mental development in postnatal interventions. One explanation offered by Brown and Pollitt and elaborated by Prado and Dewey is that better-nourished children's motor ability (fine and gross) to interact with and explore their environment could positively affect their cognitive development (4, 5). Nutrition supplements did increase exploration and activity in one study (38) but not in another (39). However, the benefits of exploration and activity accrue only if they lead to mentally challenging stimulation, which was the case in the Aburto study when the combination of macro and micronutrients enhanced exploration (fine motor manipulation of play objects) but not activity (gross body movements) (38). In sum, nutrition has the opportunity to enhance cognitive development when it supports fine motor skills that can be applied to stimulating play materials rather than gross motor skills that generate activity (38). Motor development as a mediator in the relationship between nutrition and mental development cannot be conclusively established in this review due to their concurrent measurement and future work would need to examine the temporality of this relationship; however, their significant relationship is indicative of this possibility and should be further investigated in appropriately designed interventions.

This review found no association between HAZ and mental scores effect sizes in postnatal interventions. However, a recent meta-analysis of 68 observational studies in LMIC found an association of better HAZ with earlier walking and better motor scores, and for every unit increase of HAZ prior to two years of age, an improved +0.22 standard deviation unit increase of prospective mental development was observed (40). Therefore, despite common cross-sectional findings that height and mental development are strongly correlated (1, 41-44), there is no evidence from these studies to explain why and the mechanisms warrant future investigation.

The degree of variation between studies and the limited number of prenatal trials makes it difficult to identify trends other than by intervention type. Out of all the studies included, 36% had a quality rating of strong. The majority of those rated as moderate or weak decreased their quality by not

reporting validity and reliability of their developmental measure in their context, not including study participation rates, and because of high drop-out rates.

We have added to previous systematic reviews by including more studies for pre- and postnatal nutrition, and by examining evidence for two explanatory variables, namely motor development and nutritional outcomes. This is a comprehensive meta-analysis that compiles studies using single and multiple micronutrients, as well as various fats, energy and protein. Mean effect sizes for these different nutrition interventions could be calculated for only three categories (fats/energy/protein, multiple micronutrients, single micronutrient), and suggests a trend towards greater benefit for multiple micronutrients and fats/energy/protein.

There are a number of limitations to this analysis. The control, or comparison, groups of these studies did not all receive a placebo; some received calories, multiple micronutrients or a single nutrient. The effect size from the latter type of studies is likely smaller than what it would be had the control group received a placebo. Furthermore, not all studies looked at the nutritional outcomes and motor development of the children, so sufficient evidence for this explanation is still lacking. To see an effect on mental development in children aged under-two years, supplementation may need to be provided over a longer duration. Being restricted to LMICs only, the overall small effect size could also be due to the children's lack of protein and energy, in general. This could influence growth, which would affect motor development and the children's ability to explore their environment, thus affecting their mental development (5).

Previous reviews have likewise not identified significant effects of nutrition interventions on mental development in children aged under-two years (6, 7, 12-14). Only two studies in this meta-analysis were appropriately sampled for analysis of development outcomes using the Bayley test (45, 46); to detect an effect size of 0.25 or larger (a meaningful change in development scores), a power of 0.8, and an alpha of 0.05, a sample size of 175 per group is required. Second, the tests used to measure

mental development in young children could be insensitive to the changes observed through a nutrition intervention and future studies could benefit from using tests and instruments that measure brain development and function on a finer scale (47, 48), such as functional near-infrared spectroscopy and Event-Related Brain Potential (ERP). For example, one ERP study identified memory deficits specific to infants of diabetic mothers that were not picked up by the Bayley mental test (49). A constraint in the current available data from nutrition interventions in LMICs is the lack of outcome measures outside of the traditional cognitive assessments (e.g. BSID or Griffiths Mental Development Scales). Although we limited this meta-analysis to studies in children under-two, measuring the longitudinal effect of early nutrition intervention on mental development in older ages may capture benefits not observed earlier (48). Only a few studies such as the Jamaican and Guatemalan cohorts have longitudinal measures of mental development (50-52). In the case of the Jamaican cohort, the high-energy nutrition intervention in children under two years did not confer a benefit on intelligence at 22 years of age (Walker et al., 2011). However, in the Guatemalan cohort, those exposed to a high-energy intervention in the prenatal period and the first two years of life experienced improved intellectual functioning at 27 to 33 years of age (52). It would be important for future studies to measure development over time including after the age of two years, so that this data can be included in other meta-analyses. In such studies, it would be important to do repeat measures to analyze and understand the pathways between early nutrition and subsequent development. Currently these data are highly limited in the literature from LMICs. There is also interest in combining nutrition with stimulation interventions to see whether additive or synergistic effects might be observed on mental development. Only a few studies have been appropriately designed to address this question and currently there is limited evidence on additive benefits, but more research is required on how to optimize integrated nutrition and stimulate packages of intervention (53). Other combined packages of care with nutrition also warrant further investigation (e.g., nutrition and water, sanitation, and hygiene).

This meta-analysis was done in response to the growing amount of literature and uncertainty around the effect of nutrition supplementation interventions on mental development in young children. Three promising avenues to pursue in terms of future research are identified. First, the combination of micro and macronutrients appear to be the most promising supplement in terms of its effect on mental development of young children, yet more needs to be done to investigate how variations in the study design and implementation influence the outcome. Second, the connection between nutrients and mediators of mental development, such as length, illness, temperament, and motor development need to be examined more carefully. Third, more prenatal supplementation trials are needed to establish the effect of in-utero nutritional gains on mental development. In all cases, early nutrition interventions warrant further investigation, beyond two years of age, to identify whether there is an impact in later childhood or adult functioning.

3.6 Acknowledgements

L.M.L. and A.K.Y. performed the literature review and compiled the data. LML performed the analyses and wrote the manuscript. Both authors read and approved the final manuscript. We would like to acknowledge Frances E. Aboud for her help in revising this manuscript and Emory University's Nutrition and Health Sciences Program, and the Laney Graduate School for L.M.L.'s support in pursuing her PhD.

3.7 Chapter 3 references

1. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369(9555):60-70. doi: 10.1016/s0140-6736(07)60032-4.
2. Dewey KG, Cohen RJ, Brown KH, Rivera LL. Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. The Journal of nutrition 2001;131(2):262-7.
3. Adolph KE, Tamis-LeMonda CS. The Costs and Benefits of Development: The Transition From Crawling to Walking. Child Dev Perspect 2014;8(4):187-92. doi: 10.1111/cdep.12085.
4. Brown JL, Pollitt E. Malnutrition, poverty and intellectual development. Scientific American 1996;274(2):38-43.
5. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72(4):267-84. doi: 10.1111/nure.12102.
6. Eilander A, Gera T, Sachdev HS, Transler C, van der Knaap HC, Kok FJ, Osendarp SJ. Multiple micronutrient supplementation for improving cognitive performance in children: systematic review of randomized controlled trials. The American journal of clinical nutrition 2010;91(1):115-30. doi: 10.3945/ajcn.2009.28376.
7. Ramakrishnan U, Nguyen P, Martorell R. Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions. The American journal of clinical nutrition 2009;89(1):191-203. doi: 10.3945/ajcn.2008.26862.
8. Dhingra P, Menon VP, Sazawal S, Dhingra U, Marwah D, Sarkar A, Verma P, Juyal R, Sood M, Black M. Effect of fortification of milk with zinc and iron along with vitamins C, E, A and selenium on growth, iron status and development in preschool children–a community-based double-masked randomized trial. Report from the 2nd World Congress of Pediatric Gastroenterology, Hepatology and Nutrition, 2004:3-7.
9. Faber M, Kvalsvig JD, Lombard CJ, Benade AJ. Effect of a fortified maize-meal porridge on anemia, micronutrient status, and motor development of infants. The American journal of clinical nutrition 2005;82(5):1032-9.
10. Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Stoltzfus RJ. Combined iron and folic acid supplementation with or without zinc reduces time to walking unassisted among Zanzibari infants 5- to 11-mo old. The Journal of nutrition 2006;136(9):2427-34.
11. Black MM, Baqui AH, Zaman K, Ake Persson L, El Arifeen S, Le K, McNary SW, Parveen M, Hamadani JD, Black RE. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. The American journal of clinical nutrition 2004;80(4):903-10.
12. Pasricha S-R, Hayes E, Kalumba K, Biggs B-A. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. The Lancet Global Health 2013;1(2):e77-e86.
13. Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol 2015;66:433-57. doi: 10.1146/annurev-psych-010814-015128.
14. Leung BM, Wiens KP, Kaplan BJ. Does prenatal micronutrient supplementation improve children's mental development? A systematic review. BMC pregnancy and childbirth 2011;11:12. doi: 10.1186/1471-2393-11-12.
15. Joos SK, Pollitt E, Mueller WH, Albright DL. The Bacon Chow study: maternal nutritional supplementation and infant behavioral development. Child development 1983;54(3):669-76.

16. Li Q, Yan H, Zeng L, Cheng Y, Liang W, Dang S, Wang Q, Tsuji I. Effects of maternal multimicronutrient supplementation on the mental development of infants in rural western China: follow-up evaluation of a double-blind, randomized, controlled trial. Pediatrics 2009;123(4):e685-92. doi: 10.1542/peds.2008-3007.
17. Tofail F, Kabir I, Hamadani JD, Chowdhury F, Yesmin S, Mehreen F, Huda SN. Supplementation of fish-oil and soy-oil during pregnancy and psychomotor development of infants. Journal of health, population, and nutrition 2006;24(1):48-56.
18. Beyerlein A, Hadders-Algra M, Kennedy K, Fewtrell M, Singhal A, Rosenfeld E, Lucas A, Bouwstra H, Koletzko B, von Kries R. Infant formula supplementation with long-chain polyunsaturated fatty acids has no effect on Bayley developmental scores at 18 months of age--IPD meta-analysis of 4 large clinical trials. Journal of pediatric gastroenterology and nutrition 2010;50(1):79-84. doi: 10.1097/MPG.0b013e3181acae7d.
19. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n− 3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. The American journal of clinical nutrition 2013;97(3):531-44.
20. Qawasmi A, Landeros-Weisenberger A, Bloch MH. Meta-analysis of LCPUFA supplementation of infant formula and visual acuity. Pediatrics 2013;131(1):e262-72. doi: 10.1542/peds.2012-0517.
21. Qawasmi A, Landeros-Weisenberger A, Leckman JF, Bloch MH. Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. Pediatrics 2012;129(6):1141-9. doi: 10.1542/peds.2011-2127.
22. Smithers LG, Gibson RA, McPhee A, Makrides M. Effect of long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment: a systematic review of randomized controlled trials. The American journal of clinical nutrition 2008;87(4):912-20.
23. Werker JF, Tees RC. Speech perception as a window for understanding plasticity and commitment in language systems of the brain. Developmental psychobiology 2005;46(3):233-51. doi: 10.1002/dev.20060.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 2009;151(4):264-9.
25. Jackson N, Waters E. Criteria for the systematic review of health promotion and public health interventions. Health Promotion International 2005;20(4):367-74.
26. Bayley N. Bayley Scales of Infant Development Manual. Third ed. Antonio, TX: The Psychological Corporation, 2006.
27. Griffiths RaH, M. GMDS 0-2. Griffiths Mental Development Scales – Revised: Birth to 2 Years. Oxford: Hogrefe, 1996.
28. Fagan JF, Shepard P. The Fagan test of infant intelligence. Cleveland, OH: Infantest Corporation 1986;87.
29. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. Lancet 1993;341(8836):1-4.
30. Grantham-McGregor SM, Powell CA, Walker SP, Himes JH. Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. Lancet 1991;338(8758):1-5.
31. Gurnida DA, Rowan AM, Idjradinata P, Muchtadi D, Sekarwana N. Association of complex lipids containing gangliosides with cognitive development of 6-month-old infants. Early human development 2012;88(8):595-601. doi: 10.1016/j.earlhumdev.2012.01.003.

32. Manno D, Kowa PK, Bwalya HK, Siame J, Grantham-McGregor S, Baisley K, De Stavola BL, Jaffar S, Filteau S. Rich micronutrient fortification of locally produced infant food does not improve mental and motor development of Zambian infants: a randomised controlled trial. The British journal of nutrition 2012;107(4):556-66. doi: 10.1017/s0007114511003217.
33. Nahar B, Hossain MI, Hamadani JD, Ahmed T, Huda SN, Grantham-McGregor SM, Persson LA. Effects of a community-based approach of food and psychosocial stimulation on growth and development of severely malnourished children in Bangladesh: a randomised trial. European journal of clinical nutrition 2012;66(6):701-9. doi: 10.1038/ejcn.2012.13.
34. Pollitt E, Saco-Pollitt C, Jahari A, Husaini MA, Huang J. Effects of an energy and micronutrient supplement on mental development and behavior under natural conditions in undernourished children in Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S80-90.
35. Raichle ME. Two views of brain function. Trends in cognitive sciences 2010;14(4):180-90. doi: 10.1016/j.tics.2010.01.008.
36. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. The American journal of clinical nutrition 2007;85(2):614s-20s.
37. Parviainen T, Helenius P, Poskiparta E, Niemi P, Salmelin R. Cortical sequence of word perception in beginning readers. The Journal of neuroscience : the official journal of the Society for Neuroscience 2006;26(22):6052-61. doi: 10.1523/jneurosci.0673-06.2006.
38. Aburto NJ, Ramirez-Zea M, Neufeld LM, Flores-Ayala R. The effect of nutritional supplementation on physical activity and exploratory behavior of Mexican infants aged 8-12 months. European journal of clinical nutrition 2010;64(6):644-51. doi: 10.1038/ejcn.2010.52.
39. Meeks Gardner J, Grantham-McGregor SM, Chang SM, Himes JH, Powell CA. Activity and behavioral development in stunted and nonstunted children and response to nutritional supplementation. Child development 1995;66(6):1785-97.
40. Sudfeld CR, McCoy DC, Danaei G, Fink G, Ezzati M, Andrews KG, Fawzi WW. Linear growth and child development in low- and middle-income countries: a meta-analysis. Pediatrics 2015;135(5):e1266-75. doi: 10.1542/peds.2014-3111.
41. Barros AJ, Matijasevich A, Santos IS, Halpern R. Child development in a birth cohort: effect of child stimulation is stronger in less educated mothers. International journal of epidemiology 2010;39(1):285-94. doi: 10.1093/ije/dyp272.
42. Hadley C, Tegegn A, Tessema F, Asefa M, Galea S. Parental symptoms of common mental disorders and children's social, motor, and language development in sub-Saharan Africa. Annals of human biology 2008;35(3):259-75. doi: 10.1080/03014460802043624.
43. Olney DK, Kariger PK, Stoltzfus RJ, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Pollitt E. Development of nutritionally at-risk young children is predicted by malaria, anemia, and stunting in Pemba, Zanzibar. The Journal of nutrition 2009;139(4):763-72. doi: 10.3945/jn.107.086231.
44. Servili C, Medhin G, Hanlon C, Tomlinson M, Worku B, Baheretibeb Y, Dewey M, Alem A, Prince M. Maternal common mental disorders and infant development in Ethiopia: the P-MaMiE Birth Cohort. BMC public health 2010;10:693. doi: 10.1186/1471-2458-10-693.
45. Attanasio OP, Fernández C, Fitzsimons EOA, Grantham-McGregor SM, Meghir C, Rubio-Codina M. Using the infrastructure of a conditional cash transfer program to deliver a scalable integrated early child development program in Colombia: cluster randomized controlled trial. Bmj 2014;349:g5785.
46. Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on

child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. The Lancet 2014.
47. Cheatham CL, Colombo J, Carlson SE. N-3 fatty acids and cognitive and visual acuity development: methodologic and conceptual considerations. The American journal of clinical nutrition 2006;83(6 Suppl):1458s-66s.
48. Colombo J, Carlson SE. Is the measure the message: the BSID and nutritional interventions. Pediatrics 2012;129(6):1166-7. doi: 10.1542/peds.2012-0934.
49. Nelson CA, Wewerka S, Thomas KM, deRegnier R-a, Tribbey-Walbridge S, Georgieff M. Neurocognitive sequelae of infants of diabetic mothers. Behavioral neuroscience 2000;114(5):950.
50. Martorell R, Melgar P, Maluccio JA, Stein AD, Rivera JA. The nutrition intervention improved adult human capital and economic productivity. The Journal of nutrition 2010;140(2):411-4. doi: 10.3945/jn.109.114504.
51. Walker SP, Chang SM, Vera-Hernandez M, Grantham-McGregor S. Early childhood stimulation benefits adult competence and reduces violent behavior. Pediatrics 2011;127(5):849-57. doi: 10.1542/peds.2010-2231.
52. Stein AD, Wang M, DiGirolamo A, Grajeda R, Ramakrishnan U, Ramirez-Zea M, Yount K, Martorell R. Nutritional supplementation in early childhood, schooling, and intellectual functioning in adulthood: a prospective study in Guatemala. Archives of pediatrics & adolescent medicine 2008;162(7):612-8. doi: 10.1001/archpedi.162.7.612.
53. Grantham-McGregor SM, Fernald LC, Kagawa RM, Walker S. Effects of integrated child development and nutrition interventions on child development and nutritional status. Annals of the New York Academy of Sciences 2014;1308:11-32. doi: 10.1111/nyas.12284.
54. Thilly CH. Psychomotor Development in Regions with Endemic Goiter. Edtion ed. In: Hetzel BS, Smith, R.M., ed. Fetal Brain Disorders: Recent Approaches to the Problem of Mental Deficiency. New York, NY, USA: Elsevier/North-Holland Biomedical Press, 1981:265–82.
55. Thilly CHL, R.; Roger, G.; Bourdoux, P.; Ermans, A.M. Impaired Fetal and Postanal Development and High Perinatal Death in a Severe Iodine Deficient Area. Edtion ed. In: Stockigt JR, Nagataki, S., ed. Thyroid Research VIII: Proceedings of the Eighth International Thyroid Congress, Sydney, Australia, 3–8 February, 1980. Oxford, NY, USA: Pergamon, 1980:20-3.
56. Thilly CHR, G.; Lagasse, R.; Tshibangu, D.; Vanderpas, J.B.; Berquist, H.; Nelson, G.; Ermans, A.M.; Delange, F. Fetomaternal Relationship, Fetal Hypothyroidism, and Psychomotor Retardation. Edtion ed. In: Ermans AM, Mbulamoko, N.M., Delange, F., Ahluwalia, R., ed. Role of Cassava in the Etiology of Endemic Goitre and Cretinism. Ottawa, Canada: International Development Research Centre, 1980:111–82.
57. Hamadani JD, Fuchs GJ, Osendarp SJ, Huda SN, Grantham-McGregor SM. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. Lancet 2002;360(9329):290-4. doi: 10.1016/s0140-6736(02)09551-x.
58. Schmidt MK, Muslimatun S, West CE, Schultink W, Hautvast JG. Mental and psychomotor development in Indonesian infants of mothers supplemented with vitamin A in addition to iron during pregnancy. The British journal of nutrition 2004;91(2):279-86. doi: 10.1079/bjn20031043.
59. McGrath N, Bellinger D, Robins J, Msamanga GI, Tronick E, Fawzi WW. Effect of maternal multivitamin supplementation on the mental and psychomotor development of children who are

born to HIV-1-infected mothers in Tanzania. Pediatrics 2006;117(2):e216-25. doi: 10.1542/peds.2004-1668.
60. Tofail F, Persson LA, El Arifeen S, Hamadani JD, Mehrin F, Ridout D, Ekstrom EC, Huda SN, Grantham-McGregor SM. Effects of prenatal food and micronutrient supplementation on infant development: a randomized trial from the Maternal and Infant Nutrition Interventions, Matlab (MINIMat) study. The American journal of clinical nutrition 2008;87(3):704-11.
61. Chang S, Zeng L, Brouwer ID, Kok FJ, Yan H. Effect of iron deficiency anemia in pregnancy on child mental development in rural China. Pediatrics 2013;131(3):e755-63. doi: 10.1542/peds.2011-3513.
62. Hanieh S, Ha TT, Simpson JA, Casey GJ, Khuong NC, Thoang DD, Thuy TT, Pasricha SR, Tran TD, Tuan T, et al. The effect of intermittent antenatal iron supplementation on maternal and infant outcomes in rural Viet Nam: a cluster randomised trial. PLoS medicine 2013;10(6):e1001470. doi: 10.1371/journal.pmed.1001470.
63. Ashworth A, Morris SS, Lira PI, Grantham-McGregor SM. Zinc supplementation, mental development and behaviour in low birth weight term infants in northeast Brazil. European journal of clinical nutrition 1998;52(3):223-7.
64. Beckett C, Durnin JV, Aitchison TC, Pollitt E. Effects of an energy and micronutrient supplement on anthropometry in undernourished children in Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S52-9.
65. Pollitt E. A developmental view of the undernourished child: background and purpose of the study in Pangalengan, Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S2-10.
66. Castillo-Duran C, Perales CG, Hertrampf ED, Marin VB, Rivera FA, Icaza G. Effect of zinc supplementation on development and growth of Chilean infants. The Journal of pediatrics 2001;138(2):229-35.
67. Hamadani JD, Fuchs GJ, Osendarp SJ, Khatun F, Huda SN, Grantham-McGregor SM. Randomized controlled trial of the effect of zinc supplementation on the mental development of Bangladeshi infants. The American journal of clinical nutrition 2001;74(3):381-6.
68. Black MM, Sazawal S, Black RE, Khosla S, Kumar J, Menon V. Cognitive and motor development among small-for-gestational-age infants: impact of zinc supplementation, birth weight, and caregiving practices. Pediatrics 2004;113(5):1297-305.
69. Lind T, Lonnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, Persson LA. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. The American journal of clinical nutrition 2004;80(3):729-36.
70. Taneja S, Bhandari N, Bahl R, Bhan MK. Impact of zinc supplementation on mental and psychomotor scores of children aged 12 to 18 months: a randomized, double-blind trial. The Journal of pediatrics 2005;146(4):506-11. doi: 10.1016/j.jpeds.2004.10.061.
71. Gardner JM, Powell CA, Baker-Henningham H, Walker SP, Cole TJ, Grantham-McGregor SM. Zinc supplementation and psychosocial stimulation: effects on the development of undernourished Jamaican children. The American journal of clinical nutrition 2005;82(2):399-405.
72. Aboud FE, Akhter S. A cluster-randomized evaluation of a responsive stimulation and feeding intervention in Bangladesh. Pediatrics 2011;127(5):e1191-7. doi: 10.1542/peds.2010-2160.
73. Rosado JL, Lopez P, Garcia OP, Alatorre J, Alvarado C. Effectiveness of the nutritional supplement used in the Mexican Oportunidades programme on growth, anaemia, morbidity and

cognitive development in children aged 12-24 months. Public health nutrition 2011;14(5):931-7. doi: 10.1017/s1368980010003344.

74. Siegel EH, Kordas K, Stoltzfus RJ, Katz J, Khatry SK, LeClerq SC, Tielsch JM. Inconsistent effects of iron-folic acid and/or zinc supplementation on the cognitive development of infants. Journal of health, population, and nutrition 2011;29(6):593-604.
75. Gibson RS, Kafwembe E, Mwanza S, Gosset L, Bailey KB, Mullen A, Baisley K, Filteau S. A micronutrient-fortified food enhances iron and selenium status of Zambian infants but has limited efficacy on zinc. The Journal of nutrition 2011;141(5):935-43. doi: 10.3945/jn.110.135228.
76. The Chilenje Infant Growth, Nutrition and Infection (CIGNIS) Study Team. Micronutrient fortification to improve growth and health of maternally HIV-unexposed and exposed Zambian infants: a randomised controlled trial. PLoS One 2010;5(6).
77. Phuka JC, Gladstone M, Maleta K, Thakwalakwa C, Cheung YB, Briend A, Manary MJ, Ashorn P. Developmental outcomes among 18-month-old Malawians after a year of complementary feeding with lipid-based nutrient supplements or corn-soy flour. Maternal & child nutrition 2012;8(2):239-48. doi: 10.1111/j.1740-8709.2011.00294.x.
78. Phuka JC, Maleta K, Thakwalakwa C, Cheung YB, Briend A, Manary MJ, Ashorn P. Postintervention growth of Malawian children who received 12-mo dietary complementation with a lipid-based nutrient supplement or maize-soy flour. The American journal of clinical nutrition 2009;89(1):382-90. doi: 10.3945/ajcn.2008.26483.
79. Surkan PJ, Siegel EH, Patel SA, Katz J, Khatry SK, Stoltzfus RJ, Leclerq SC, Tielsch JM. Effects of zinc and iron supplementation fail to improve motor and language milestone scores of infants and toddlers. Nutrition (Burbank, Los Angeles County, Calif) 2013;29(3):542-8. doi: 10.1016/j.nut.2012.09.003.
80. Singla DR, Shafique S, Zlotkin SH, Aboud FE. 25-element micronutrient powder benefits language but not cognition in Bangladeshi full term low birth weight children1. Journal of Nutrition 2014.
81. Colombo J, Zavaleta N, Kannass KN, Lazarte F, Albornoz C, Kapa LL, Caulfield LE. Zinc Supplementation Sustained Normative Neurodevelopment in a Randomized, Controlled Trial of Peruvian Infants Aged 6–18 Months. The Journal of nutrition 2014:jn. 113.189365.

Table 3.1: Prenatal intervention studies

Reference	Sample size analyzed, ages at base and endline	Design	Main Development outcomes				Quality	
			Mental Development (mean±SD)	d	Motor Development (mean±SD)	d	Item Ratings	Global Rating
Thilly et al. 1980a DR Congo HDI .304 (54-56)	N=75 INT n=39 CTRL n=36 Mother's enrolled in 2nd and 3rd trimester Infants tested at 23 months.	RCT where Intervention received a single dose of 475mg iodine in oil and Control received a placebo.	*Brunet-Lézine:* INT (115±18) > CTRL (103±24)**	0.57			W, S, S, S, W, W, S, M	Weak
Joos et al. 1983 Taiwan HDI .699 (15)	N=198 INT n=99 CTRL n=99 Mothers enrolled during lactation of first pregnancy Infants from second pregnancy tested at 8m Mean base maternal BMI=20.4kg/m^2	RCT where Intervention received a high calorie and protein supplement (800kcal and 40g protein per day). Control received placebo with 6kcal or 80kcal per day. They were in liquid form. A vitamin and mineral pill was given to all women. Supplementation during lactation of first child and continued through interpregnancy, pregnancy and lactation of second child. This analysis used children from the second pregnancy only.	*BSID:* INT (4.48±1.8) = CTRL (4.39±1.8)	0.05	*BSID:* INT (3.8±1.9) = CTRL (3.31±1.71)	0.27	M, S, S, S, W, S, M, S	Moderate
Hamadani et al. 2002 Bangladesh HDI .515 (57)	N=168 INT n=83 CTRL n=85 Women started supplementation at 4m gestation Infants tested at 13m Mean base maternal BMI=18.7kg/m^2	RCT where Intervention received daily zinc supplementation (30mg zinc acetate tablets) and Control received a placebo.	*BSID II:* INT (99.34±11.2) < CTRL (102.64±10.0)*	-0.31	*BSID II:* INT (88.7±17.4) < CTRL (95.7±15.0)**	-0.43	M, S, S, S, S, M, S, S	Strong
Schmidt et al. 2004 Indonesia HDI .629 (58)	N=188 INT n=94 CTRL n=94 Women enrolled at 16-20wks gestation Infants measured at 12m	RCT where Intervention received weekly supplementation of 120mg Fe + 500mcg FA + 4800mcg retinol in the form of retinyl acetate and Control received 120mg Fe + 500mcg FA.	*BSID:* INT (105.4±22.3) = CTRL (104.0±27.1)	0.06	*BSID:* INT (98.3±32.0) = CTRL (102.3±36.8)	-0.12	M, S, S, S, W, S, S, S	Moderate

	Mean base maternal BMI=22.0kg/m^2							
Tofail et al. 2006 Bangladesh HDI .515 (17)	N=249 INT n=125 CTRL n=124 Mothers supplemented in last trimester Infants tested at 10m Mean base maternal BMI=20.3kg/m^2	RCT where Intervention received daily supplementation of 4g of fish oil (containing 1.2 g of docosahexaenoic acid and 1.8 g of eicosapentaenoic acid) and Control received 4g of daily soy-oil (containing 2.25g of linoleic acid and 0.27g of α-linolenic acid).	*BSID II:* INT (102.5±8.0) = CTRL (101.5±7.8)	0.13	*BSID II:* INT (101.7±10.9) = CTRL (100.5±10.1)	0.11	M, S, S, S, S, S, S, S	Strong
McGrath et al. 2006 Tanzania HDI .476 (59)	N=334 Multivitamin n=93 No multivitamin n=74 Vitamin A n=94 No vitamin A n=73 Mothers enrolled at 12-27 wks gestation Infants measured at 18m HIV-infected mothers	RCT where Interventions received daily vitamin A (30 mg of β-carotene + 5000 IU preformed vitamin A), multivitamins with no vitamin A (20mg B1, 20mg B2, 25mg B6, 100mg niacin, 50 mcg B12, 500 mg vitamin C, 30 mg vitamin E, and 0.8mg FA), or multivitamins+vitamin A, and Control received placebo.	*BSID II:* INT MV (78.4±13.8) = CTRL No MV (82.0±13.5) INT Vit A (80.6±12.5) = CTRL No vit A (79.3±15.4)	-0.26 0.09	*BSID II:* INT MV (86.2±14.3)= CTRL No MV (88.5±14.8) INT Vit A (87.4±12.2) = CTRL No vit A (87.0±15.1)	-0.16 0.03	M, S, S, S, W, S, S, S	Moderate
Tofail et al. 2008 Bangladesh HDI .515 (60)	N=1407 INT MMN n=705 CTRL n=702 Mother enrolled btw 6-8 weeks of pregnancy. Infants measured at 7m Mean base maternal BMI=20.2kg/m^2	RCT where Intervention received daily MMN and Control received iron and folate. MMN included 150mcg I (potassium iodide), 15mg Zn (sulfate), 65mcg Se (sodium selenite), 2mg Cu (sulfate), 800mcg retinyl acetate (RE) vitamin A, 1.4mg thiamine mononitrate, 1.4mg vitamin riboflavin, 18mg vitamin B3 (niacin), 1.9mg vitamin B6 (pyridoxine hydrochloride), 2.6mcg vitamin B12 (cyanocobalmin), 70mg vitamin C, 200 IU vitamin D (vitamin D3), and 10mcg vitamin E (α -tocopherol acetate) in the recommended dietary allowance dose in addition to 60mg Fe (fumarate) and 400mcg folate. Control received 30mg Fe (fumarate) and 400mcg folate.	*Problem solving test:* *Support:* INT MMN (11.3±7.9) = CTRL (11.1±7.5)	0.03	*BSID II:* *INT* MMN (103.66±16.6) = CTRL (102.42±15.4)	0.08	S, S, S, W, M, S, S	Moderate

Li et al. 2009 China HDI .699 (16)	N=1159 INT Fe/FA n=393 INT MMN n=351 CTRL n=415 Mean gestation age of mothers at enrollment=97.36days Infants measured at 12m Mean base maternal BMI=20.8kg/m^2	Cluster RCT where Interventions received MMN, iron/folic acid, or folic acid supplementation. Assume 2 trimesters of supplementation. Control received folic acid. MMN included 30mg iron, 400mcg folate, 15mg zinc, 2mg copper, 65mcg selenium, 150mcg iodine, 800mcg vitamin A, 1.4mg vitamin B1, 1.4mg vitamin B2, 1.9mg vitamin B6, 2.6mcg vitamin B12, 5mcg vitamin D, 70mg vitamin C, 10mg vitamin E, and 18mg niacin. FE/FA included 60mg iron and 400mcg folic acid. FA included 400mcg folic acid.	*BSID:* INT Fe/FA (102.44±45.26) = CTRL (102.65±49.21) INT MMN (103.65±42.11) = CTRL (102.65±49.21)	0.04 0.02	*BSID:* INT Fe/FA (45.3±22.15) = CTRL (45.39±22.40) INT MMN (45.64±19.83) = CTRL (45.39±22.40)	-0.004 0.01	S, S, S, S, W, M, S, S	Moderate
Chang et al. 2013 China HDI .699 (61)	N=850 INT Fe/FA n=238 INT MMN n=254 CTRL n=313 Mean gestation age of mothers at enrollment=97.36days Infants measured at 24m Mean base maternal BMI=20.8kg/m^2	Cluster RCT where Interventions received MMN, iron/folic acid, or folic acid supplementation. Assume 2 trimesters of supplementation. Control received folic acid. MMN included 30mg iron, 400mcg folate, 15mg zinc, 2mg copper, 65mcg selenium, 150mcg iodine, 800mcg vitamin A, 1.4mg vitamin B1, 1.4mg vitamin B2, 1.9mg vitamin B6, 2.6mcg vitamin B12, 5mcg vitamin D, 70mg vitamin C, 10mg vitamin E, and 18mg niacin. FE/FA included 60mg iron and 400mcg folic acid. FA included 400mcg folic acid.	*BSID II:* INT Fe/FA (90.31 ± 16.1) = CTRL (88.78 ± 17.3) INT MMN (89.67 ± 19.5) = CTRL (88.78 ± 17.3)	0.09 0.05	*BSID II:* INT Fe/FA (104.47 ± 11.7) = CTRL FA (103.89 ± 12.8) INT MMN (103.13 ± 13.0) = CTRL FA (103.89 ± 12.8)	0.05 -0.06	S, S, S, W, M, S, S	Moderate
Hanieh et al. 2013 Viet Nam HDI .617 (62)	N=769 INT n=381 CTRL n=388 Mothers enrolled if <16wks gestation Infants tested at 6m Mean base maternal BMI=19.9kg/m^2	Cluster RCT where Intervention received MMN twice per week and Control received 60mg elemental iron plus 0.4mg folic acid daily. MMN contained 15 micronutrients, including 60mg iron, 20mg zinc, 300mcg iodine, 4mg copper, 130mcg selenium, 1.6mg vitamin A, 2.8mg thiamine, 2.8mg riboflavin, 36mg niacin, 3.8mg vitamin B6, 5.2 mcg vitamin B12, 1.5mg folic acid, 140mg vitamin C, 400 IU vitamin D, and 20mg vitamin E.	*BSID III:* INT (101.2±9.9) = CTRL (100.2±11.4)	0.09			S, S, S, S, W, S, S, S	Moderate

Note: Assessment of Quality (Item Ratings) with following categories in order: Selection Bias, Study Design, Confounders, Blinding, Data Collection Methods, Withdrawals and Dropouts, Intervention Integrity, Analysis; HDI (Human Development Index); RCT (Randomized Controlled Trial); m (month); wk (week); INT (Intervention group); CTRL (Control group); BMI (Body Mass Index); BSID (Bayley Scales of Infant Development); Effect Size d (Standardized Mean Difference); SD (Standard deviation); *p<0.05; **p<0.01; ***p<0.001; W (Weak), M (Moderate), S (Strong); MMP (Multiple Micronutrient Powder); MMN (Multiple micronutrients); MV (Multivitamin); Zn (Zinc); Fe (Iron); FA (Folic Acid)

Table 3.2: Postnatal intervention studies

				Main developmental outcomes						Quality	
Reference	**Sample size analyzed, ages at base and endline**	**Design**	**Duration (m)**	**Mental Development (mean ± SD)**	**Effect Size d**	**Motor Development (mean ± SD)**	**Effect Size d**	**Growth parameters (mean ± SD)**	**Effect Size d**	**Item Ratings**	**Global Rating**
Grantham-McGregor et al. 1991 Jamaica HDI .731 (30)	N=65 INT n=32 CTRL n=33 Base age=9-24m with mean=18m End age=33-48m with mean=24m Mean base HAZ=-2.9	RCT where Intervention received milk-based formula 750kcal and 20gprotein/day and Control received no supplement.	24	*Griffiths Mental Scales:* INT (86±10) = CTRL (83±10)	0.30	*Griffiths Mental Scales:* INT (97±13) = CTRL (95±11)	0.17			M, S, S, S, S, M, M	Strong
Idjradinata & Pollitt. 1993 Indonesia HDI .629 (29)	N=44 INT n=22 CTRL n=22 Base age=12-18m End age=16-22m Iron-sufficient infants	RCT where Intervention received ferrous sulphate 3mg/kg per day in syrup form and Control received a placebo syrup.	4	*BSID:* INT (109.1±2.2) = CTRL (106.8±2.3)	1.02	*BSID:* INT (108.7±2.1) = CTRL (108.3±2.1)	0.19			M, S, S, S, W, S, S, M	Moderate
Ashworth et al. 1998 Brazil HDI .730 (63)	N=138 INT 1mgZn n=48 INT 5mg Zn=48 CTRL n=44 LBW term infants. Base age=0m End age=12m	Prospective double-blind part-RCT where two Intervention groups received 1mg or 5mg Zn (as zinc sulphate) daily (except Sundays) and Control received placebo. Injected liquid Zn/placebo with syringe.	2	*BSID:* INT 1mg Zn (101.1±11.0) = CTRL (100.4±11.3) INT 5mg Zn (100.0±11.6) = CTRL (100.4±11.3)	0.06 -0.03	*BSID:* INT 1mgZn (106.7±11.1)=CTRL (109.1±12.2) INT 5mgZn (106.9±12.1)=CTRL (109.1±12.2)	-0.21 -0.18			M, M, S, S, W, M, S, S	Moderate
Pollitt et al. 2000 Indonesia HDI .629 (34,64,65)	N =75 INT n=38 CTRL n=37 Base age=12 m End age=24m Base HAZ≤-1	Cluster RCT where Intervention given daily high energy + Fe (E) (1171 kJ + 12mg iron) or given Fe with low energy (M) (12mg iron + 209 kJ). Control given skim milk only (209 kJ). MMN tablet included 8 micronutrients, in tablet form (doses of micronutrients other than iron not identified). High Energy drink was condensed milk vs low energy skim milk.	12	*BSID I:* INT M+E (151.3 ± 6.0) = CTRL (149.3 ± 8.0)	0.28					W, S, W, M, W, W, S, M	Weak

Castillo-Duran et al. 2001 Chile HDI .819 (66)	N=112 term neonates; INT n=57 CTRL n=55 Base age=newborn End age=12m	RCT where intervention group was given 5mg/d supplemental zinc within 20 days of birth, and then monthly until 1 year. Control group was given a lactose placebo. All received iron 1 to 2 mg/kg/d after 5mo.	12	*BSID II:* At 12m: INT (90.9±10.5) = CTRL (88.9±9.1)	0.20	*BSID II:* At 12m: INT (84.5±11.5) = CTRL (87.6±9.9)	-0.29	*WAZ:* At 12 m: INT (-0.23±1.04) = CLT (0.22±0.86) *HAZ:* At 12 m: INT (-0.44±0.94) = CTRL (-0.07±0.75)	-0.47 -0.60	M, S, S, S, W, M, S, M	Moderate
Hamadani et al. 2001 Bangladesh HDI .515 (67)	N = 198 INT n=97 CTRL n=101 Base age mean=1.4 m End age mean=13.6 m Mean base HAZ=-1.1	RCT where Intervention received daily 5mg Zn and Control received placebo syrup.	6	*BSID II:* INT (103.1 ± 11.0) < CTRL (106.4 ± 9.3)*	-0.33	*BSID II:* INT (88.0 ± 18.9) = CTRL (90.6 ± 18.9)	-0.14	*WAZ:* INT (-2.4±0.9) = CTRL (-2.5±0.9) *HAZ:* INT (-2.3±1.0) = CTRL (-2.4±1.0)	0.11 0.10	M, S, S, S, S, M, S, S	Strong
Black et al. 2004a Bangladesh HDI .515 (11)	N=221 INT MMN n=35 INT Zn+Fe n=43 INT Fe n=47 INT Zn n=49 CTRL (riboflavin) n=45 Base age 6.5 m End age 12.7 m Mean base HAZ=-1.2	RCT where Intervention received 16 MMN compared with Control (riboflavin) and with iron & zinc separately and together. INT MMN: 2xRDA thiamine, niacin, FA, pantothenic acid, iodine, copper, manganese, selenium, and Vitamins C, D, E, B6, B12 + 20mgFe + 20mgZn INT Zn+Fe: 20mg Zn sulphate + 20mg Fe sulphate INT Fe: 20mg Fe sulfate INT Zn: 20mg Zn acetate CTRL: 1mg riboflavin	6	*BSID II:* Fe (104.3 ± 9.5) = CTRL (102.7 ± 13.5) Zn (104.7 ± 8.3) = CTRL (102.7 ± 13.5) Fe+Zn (105.4 ± 11.6) = CTRL (102.7 ± 13.5) MMN (104.3 ± 13.0) = CTRL (102.7 ± 13.5)	0.14 0.18 0 .12 0.22	*BSID II:* Fe (99.5 ± 16.6) = CTRL (95.4 ± 16.3) Zn (101.2 ± 16.6) = CTRL (95.4 ± 16.3) Fe+Zn (103.7 ± 16.2)= CTRL (95.4 ± 16.3) MMN (104.5 ± 16.5) = CTRL (95.4 ± 16.3)	0.25 0.35 0.51 0.55	*WAZ:* Fe (-2.2±1.0) = CTRL (-2.0±1.2) Zn (-2.0±1.2) = CTRL (-2.0±1.2) Fe+Zn (-2.2±1.3) = CTRL (-2.0±1.2) MMN (-2.1±1.0) = CTRL (-2.0±1.2) *HAZ:* Fe (-1.6±0.9) = CTRL (-2.0±1.2) Zn (-1.6±0.9) = CTRL (-2.0±1.2) Fe+Zn (-1.8±0.9) = CTRL (-1.7±1.0) MMN (-1.7±0.8) = CTRL (-1.7±1.0)	-0.18 0 -0.16 -0.09 0.38 0.38 -0.11 0	S, S, S, S, S, M, S, M	Strong

Black 2004 India HDI .554 (68)	N = 162 INT MMN+Zn n= 85 CTRL MMN n= 77 Base age=1m End age=10m Mean base HAZ=-1.9 All newborns small-for-gestational age, <10th percentile weight, term	RCT where 5 MMN+Zn group compared with 5 MMN group. Syrup with MMN fed directly to children daily. MMN includes 0.5mg/d riboflavin, 180mg/d calcium, 90mg/d phosphorus, 60mol/d folate, and 10 mg/d iron, with 5mg of zinc sulfate.	9	*BSID II:* INT MMN+Zn (86.2 ± 4.9) = CTRL MMN (86.4 ± 5.1)	0.04	*BSID II:* INT MMN+Zn (91.7 ± 9.8) = CTRL MMN (91.5 ± 14.2)	0.020			S, S, S, S, S, S, S, S	Strong
Lind et al. 2004 Indonesia HDI .629 (69)	N= 650 INT Fe n=163 INT Zn n=162 INT Fe+Zn n=161 CTRL n=164 Base age=6m End age=12m Mean base HAZ=-0.3	RCT where Intervention received daily supplementation with 10mg Fe, or 10mg Zn, or both, and Control received placebo syrup.	6	*BSID II:* INT Fe (101 ± 9.7) = CTRL (99 ± 10.0) INT Zn (101 ± 9.3) = CTRL (99 ± 10.0) INT Zn+Fe (100 ± 9.8) = CTRL (99 ± 10.0)	0.20 0.21 0.10	*BSID II:* INT Fe (106 ± 11.0) > CTRL (103 ± 10.8)* INT Zn (105 ± 10.6) = CTRL (99 ± 10.0) INT Zn+Fe (103 ± 10.3) = CTRL (99 ± 10.0)	0.27 0.58 0.39	*WAZ:* INT Zn (-1.46±1.8) < CTRL (-1.72±1.00)* INT Fe (-1.65±1.08) = CTRL (-1.72±1.00) INT Fe+Zn (-1.68±1.02) = CTRL (-1.72±1.00) *HAZ:* INT Fe (-0.66±0.91) = CTRL (-0.81±0.86) INT Zn (-0.77±0.92) = CTRL (-0.81±0.86) INT Fe+Zn (-0.90±0.90) = CTRL (-0.81±0.86)	0.18 0.06 0.04 0.17 0.04 -0.10	S, S, S, S, W, S, S, S	Moderate
Taneja et al. 2005 India HDI .554 (70)	N = 571 INT n=283 CTRL n= 288 Base age=12-18m with mean=14.9 m End age=16-24 m with mean=21 m Base stunting=36.8%	RCT where Intervention received daily 20mg zinc (10mg for infants) and Control received placebo.	4	*BSID II:* INT (92.8 ± 10.9) = CTRL (91.3 ± 10.8)	0.14	*BSID II:* INT (93.9 ± 11.8) = CTRL (92.2 ± 11.4)	0.15			S, S, S, S, S, S, M, M	Strong

Gardner et al. 2005 Jamaica HDI .731 (71)	N=114 INT n=55 CTRL n=59 Base age=9-30m End age=15-36m Mean base HAZ=-1.4	Cluster RCT where Intervention received 10mg Zn daily with/out stimulation and Control received placebo with/out stimulation, All children received 0.5mL of 10 MMN including 1500 IU vitamin A, 400 IU vitamin D, 0.5mg vitamin B1, 0.8mg riboflavin, 7mg nicotinamide, 1mg vitamin B6, 30mg vitamin C, 8mg iron, 1mg folic acid, 2mg vitamin B12.	6	*Griffiths Mental Scales:* Cognitive INT (89.45 ± 12.8) = CTRL (89.85 ±11.8)	-0.03	Griffiths Mental Scales: Locomotor INT (97.4 ± 12.7) = CTRL (102.6 ±9.9)	-0.46	WAZ: INT (-2.04±0.56) = CTRL (-2.03±0.58) HAZ: INT (-1.26±0.71) = CTRL (-1.08±0.80)	-0.02 -0.24	M, S, S, S, S, S, S, S	Strong
Aboud & Akhter 2011 Bangladesh HDI .515 (72)	N = 186 INT n=99 CTRL n=85 Base age mean=14 m End age mean=21 m Mean base HAZ=-1.6	Cluster RCT where Intervention received MMP (containing 12.5mg of iron, 300mcg of vitamin A, 150mcg of folic acid, 50 mg of vitamin C, and 5mg of zinc) plus 6-session parenting program on stimulation and Control received parenting program but no MMP.	7	*BSID II:* Language: INT (30.89 ± 21.2) = CTRL (32.7 ± 21.3)	-0.09			*WAZ:* INT (-1.87 ± 1.0) > CTRL (-2.03 ± 1.0)* *HAZ:* INT (-1.89 ± 1.1) = CTRL (-1.99 ± 1.1)	0.16 0.09	M, S, S, M, S, S, S, S	Strong
Rosado et al. 2011 Mexico HDI .775 (73)	N = 186 INT n= 55 CTRL n=61 Base age=12-24m with mean=22.4 m End age18-30m with mean=28 m Mean base HAZ=-1.2	RCT where Intervention received daily supplement (44g MMP daily, consisting of 194 kcal, 815 kJ, 6g protein, 7g fat, 28g carbohydrates, 25mg sodium, 10mg iron, 10mg zinc, 400 mcg vitamin A, 6mg vitamin E, 40mg vitamin C, 0.7mcg vitamin B12, 50mcg folic acid, 0.8mg riboflavin) and Control received placebo (174 kcal, 731 kJ, 30g carbohydrates). Half-supplement group excluded here.	6	*BSID II:* INT (135.9 ± 13.7) = CTRL (137.6 ± 12.6)	-0.13	*BSID II:* INT (88.6± 9.2) = CTRL (90.0 ± 9.3)	-0.15	*WAZ:* INT (-0.7 ± 0.9) = CTRL (-0.7 ± 1.0) *HAZ:* INT (-1.1 ± 1.0) = CTRL (-1.0 ± 1.1)	0 -0.10	S, S, S, M, W, S, S, M	Moderate
Siegel et al. 2011 Nepal HDI .463 (74)	N = 325 INT Zn n= 80 INT Fe+FA n=80 INT MMN n=80 CTRL n= 81 Base age 1-35wk with mean= 7m End age mean=19m Base stunting=16.7%	Cluster RCT with 3 INTs (daily supplement with Zn, Fe or both) and Control received a placebo. INT Zn: 5mg/d Zn INT Fe + FA: 6.25mg/d Fe; 25mcg/d FA INT MMN: 5mg/d Zn + 6.25mg/d Fe + 25mc/d FA	12	*Fagen Test of Infant Intelligence:* Fixation time: INT Zn (1.31 ± 0.2) = CTRL (1.30 ± 0.21) INT Fe + FA (1.30 ± 0.4) = CTRL (1.30 ± 0.21) INT MMN (1.32 ± 0.2) = CTRL (1.30 ± 0.21)	0.05 0 0.10			WAZ: INT Zn (-1.52±1.04) = CTRL (-1.99±1.00) INT Fe+FA (-1.83±0.92) = CTRL (-1.99±1.00) INT MMN (-1.75±1.10) = CTRL (-1.99±1.00) HAZ: INT Zn (-0.95±0.98) = CTRL (-1.64±0.93) INT Fe+FA (-	0.46 0.17 0.23 0.72	M, S, S, S, W, M, S, S	Moderate

								1.34±0.93) = CTRL (-1.64±0.93) INT MMN (-1.40±1.09) = CTRL (-1.64±0.93)	0.32 0.24		
Gurnida et al. 2012 Indonesia HDI .629 (31)	N=59 INT n=29 CTRL n=30 Base age 2-8 wk with mean=3.8 wk End age 24 wk Mean base HAZ=-0.4	RCT where Intervention given formula with 9mg/100g gangliosides for up to 6 months. Controls given standard formula milk with 6mg/100g.	6	*Griffiths Mental Development Scale:* Cognitive: INT (131.1 ± 14.8) > CTRL (123.2 ± 16.0)***	0.53	*Griffiths Mental Development Scale:* Gross (Locomotive) motor: INT (120.0±12.23) = CTRL (117.±16.91)	0.20			M, S, S, S, W, S, S, M	Moderate
Manno et al. 2012 Zambia HDI .448 (32,75,76)	N=335 INT n=160 CTRL n=175 Base age=6 m End age=18 m Mean base HAZ=-0.8 38% of mothers were HIV+; 3.9% of children were HIV+	RCT where Intervention given richly fortified porridge flour and Controls given standard fortified flour. INT flour was fortified with 18 micronutrients (6.5mg vitamin A, 2g vitamin c, 0.1mg vitamin D, 9mg thiamin, 11mg riboflavin, 140mg niacin, 9mg pyridoxine, 2mg folate, 10mcg vitamin B12, 40mg pantothenic acid, 1g magnesium oxide, 250mg iron, 200mg zinc, 3mg copper, 12mg manganese, 0.2mg selenium, 7g calcium, 5g phosphorus).	12	*BSID II:* INT (89.8 ± 7.4) = CTRL (88.4 ± 7.4)	0.19	*BSID II:* INT (90.0 ± 6.2) < CTRL (91.4 ± 6.1)*	-0.23	*HAZ:* INT (-1.05 ± 1.2) = CTRL (-1.12 ± 1.11)	0.06	M, S, S, S, S, M, S, S	Strong
Nahar et al. 2012 Bangladesh HDI .515 (33)	N=136 INT n=77 CTRL n=59 Base age=6-24m End age=12-30m Mean base HAZ=-3.5	RCT where Intervention received food supplementation (FS) and control received growth monitoring, health education, and micronutrient supplementation. FS consisted of roasted rice powder 20 g, roasted lentil powder 10 g, molasses 5 g and soya oil 3 g, to provide 150 kcal (~630 kJ) of energy with 11% of the energy derived from protein. Both groups received multivitamin drops with a daily dose of 1ml providing vitamin-A, vitamin-D, thiamin, riboflavin, pyridoxine, nicotinamide, calcium, ascorbic acid and zinc sulphate, and from weeks 2–12, iron and folic acid were provided as standard treatment of severe malnutrition (micronutrient doses were not specified).	6	*BSID II:* INT (67.9±14.4) = CTRL (66.7±13.6)	0.09	*BSID II:* INT (66.2±15.2) = CTRL (69.4±16.4)	-0.20	*WAZ:* INT (-3.4±0.8) = CTRL (-3.2±1.1) *HAZ:* INT (-3.9±1.1) = CTRL (-4.1±1.0)	-0.21 0.40	W, S, S, S, S, M, S, S	Moderate

Phuka et al. 2012 Malawi HDI .418 (77,78)	N= 163 INT n=51 CTRL n=56 Base age=6 m End age=18 m Mean base HAZ=-1.6	RCT where Intervention given daily 50g lipid-based spread fortified with 17 vitamins and minerals (256 kcal, 7g protein, 14g carbohydrate, 17g fat, 400mcg retinol, 160mcg folate, 6mg niacin, 2mg pantothenic acid, 0.5mg riboflavin, 0.5mg thiamin, 0.5mg vitamin B6, 0.9mcg vitamin B12, 30mg vitamin C, 5mcg vitamin D, 283 mg calcium, 0.4mg copper, 135mcg iodine, 8mg iron, 60mg magnesium, 17mcg selenium, 8mg zinc). Controls given daily 71g corn-soy flour with fewer micronutrients.	12	*Griffiths Mental Development:* Cognitive: INT (18.25 ± 2.41) = CTRL (18.41 ± 2.31)	-0.07	*Griffiths Mental Development:* Gross motor (Locomotive): INT (15.81 ± 0.78) = CTRL (15.91 ± 0.98)	-0.11	*WAZ:* INT (-0.62±1.04) = CTRL (-1.74±1.07) *HAZ:* INT (-1.57±1.01) = CTRL(-1.64±0.82)	1.06 0.08	M, S, S, M, S, S, M, S	Strong
Surkan et al. 2013 Nepal HDI .463 (79)	N=569 INT Zn n= 127 INT Fe+FA n=129 INT 3 MMN n=161 CTRL n= 152 Base age=4-17m End age=16-29m	Cluster randomized trial with 3 Interventions with daily supplement with Zn, Fe or both, and Control received placebo. INT Zn: 10mg/d zinc INT Fe + FA: 12.5mg/d Fe; 50 mcg/d FA INT 3 MMN (Zn + Fe + FA) Children <1yr received half-dose of supplement.	12	*Fagen Test of Infant Intelligence:* Language score: INT Zn (10.2±3.39) = CTRL No Zn (10.35±2.92) INT Fe (10.2±3.38) = CTRL No Fe (10.25±2.93)	-0.05 -0.02	*Griffiths Mental Development Scale and the MacArthur Communicative Development Inventory:* INT Zn (23.8±6.5) = CTRL No Zn (24.2±6.5) INT Fe (24.1±6.5) = CTRL No Fe (24.0±6.5)	-0.06 0.015			S, S, S, S, W, S, S, M	Moderate
Yousafzai et al. 2014 Pakistan HDI .515 (46)	N=680 INT n=334 CTRL n=346 Base age=0-2.5m End age=24m Mean base HAZ=-1.0	Cluster RCT, factorial design where Intervention received nutrition education and MMP and Control received standard care. MMP comprised of iron, folate, vitamin A and vitamin C (doses not specified).	24	*BSID III:* Cognition: INT (76.5 ± 22.2) > CTRL (71.9 ± 18.0)***	0.20	*BSID III:* INT 87.8 (22.6) > CTRL 81.9 (20.7)***	d=0.20			S, S, S, S, W, S, S, S	Moderate
Singla et al. 2014 Bangladesh HDI .515 (80)	N=186 INT n=99 CTRL n=87 Base age=7-12m End age=16-22m LBW children Mean base HAZ=-2.0	RCT where Intervention received daily 22-element MMP plus education and control received education only. MMP contained 300mcg vitamin A, 5mcg vitamin D, 6mg vitamin E, 30mg vitamin C, 0.5mg vitamin B1, 0.5mg vitamin B2, 0.5mg vitamin B6, 0.5mcg vitamin B12, 6mg niacin, 160mcg FA, 10mg Fe, 10mg Zn, 0.5mg copper, 20mcg selenium, 90mcg iodine, 100mg calcium, 20mg magnesium, 100mg phosphorus, 0.6mg	6	*BSID III:* Cognition: INT (51.2±4.66) = CTRL (50.67±4.31)	0.08					S, S, S, S, S, S, S, S	Strong

		manganese, 20mcg vitamin K, 1.8mg pantothenic acid, 6mcg biotin).									
Attanasio et al. 2014 Colombia HDI .719 (45)	N=626 INT n=308 CTRL n=318 Base age=12-24m End age=20-42m Base stunting=13.0%	Cluster RCT where Intervention group received micronutrient sprinkles and Control group received nothing. Sprinkles contained 12.5mg iron, 5mg zinc, vitamin A 300mcg retinol equivalents, 160mcg folic acid, and 30mg vitamin C.	18	*BSID III:* Cognition: INT (71.63±4.26) = CTRL (71.68±4.38)	-0.01	*BSID III:* Gross Motor: INT (63.19±2.99) = CTRL (63.31±2.79)	-0.04			M, S, S, S, W, S, S, S	Moderate
Colombo et al. 2014 Peru HDI .741 (81)	N=249 INT n=128 CTRL n=121 Base age=6m End age=18m Mean base HAZ=-0.5	RCT where Intervention group received a daily liquid supplement containing 10mg/d of zinc (zinc sulfate), 10mg/d of iron (ferrous sulfate), and 0.5mg/d of copper (copper oxide), and Control group received an identical daily liquid supplement containing only 10mg/d of iron and 0.5mg/d of copper.	12	*BSID II:* INT (94.98±6.95) = CTRL (94.43±6.76)	0.08	*BSID II:* INT (104.10±5.77) = CTRL (103.92±6.10)	0.03	*WAZ:* INT (0.1±0.9) = CTRL (0.1±0.8) *HAZ:* INT (-0.5±1.0) = CTRL (-0.6±0.9)	0 0.11	S, S, S, S, W, S, S, S	Moderate

Note: Assessment of Quality (Item Ratings) with following categories in order: Selection Bias, Study Design, Confounders, Blinding, Data Collection Methods, Withdrawals and Dropouts, Intervention Integrity, Analysis; HDI (Human Development Index); RCT (Randomized Controlled Trial); m (month); wk (week); INT (Intervention group); CTRL (Control group); HAZ (Height-for-age z-score); BSID (Bayley Scales of Infant Development); Effect Size d (Standardized Mean Difference); SD (Standard deviation); RDA(Recommended Dietary Allowance); *p<0.05; **p<0.01; ***p<0.001; W (Weak), M (Moderate), S (Strong); MMP (Multiple Micronutrient Powder); MMN (Multiple micronutrients); MV (Multivitamin); Zn (Zinc); Fe (Iron); FA (Folic Acid)

Figure 3.1: Selection of studies for the systematic review of the effect of nutritional interventions on child mental development

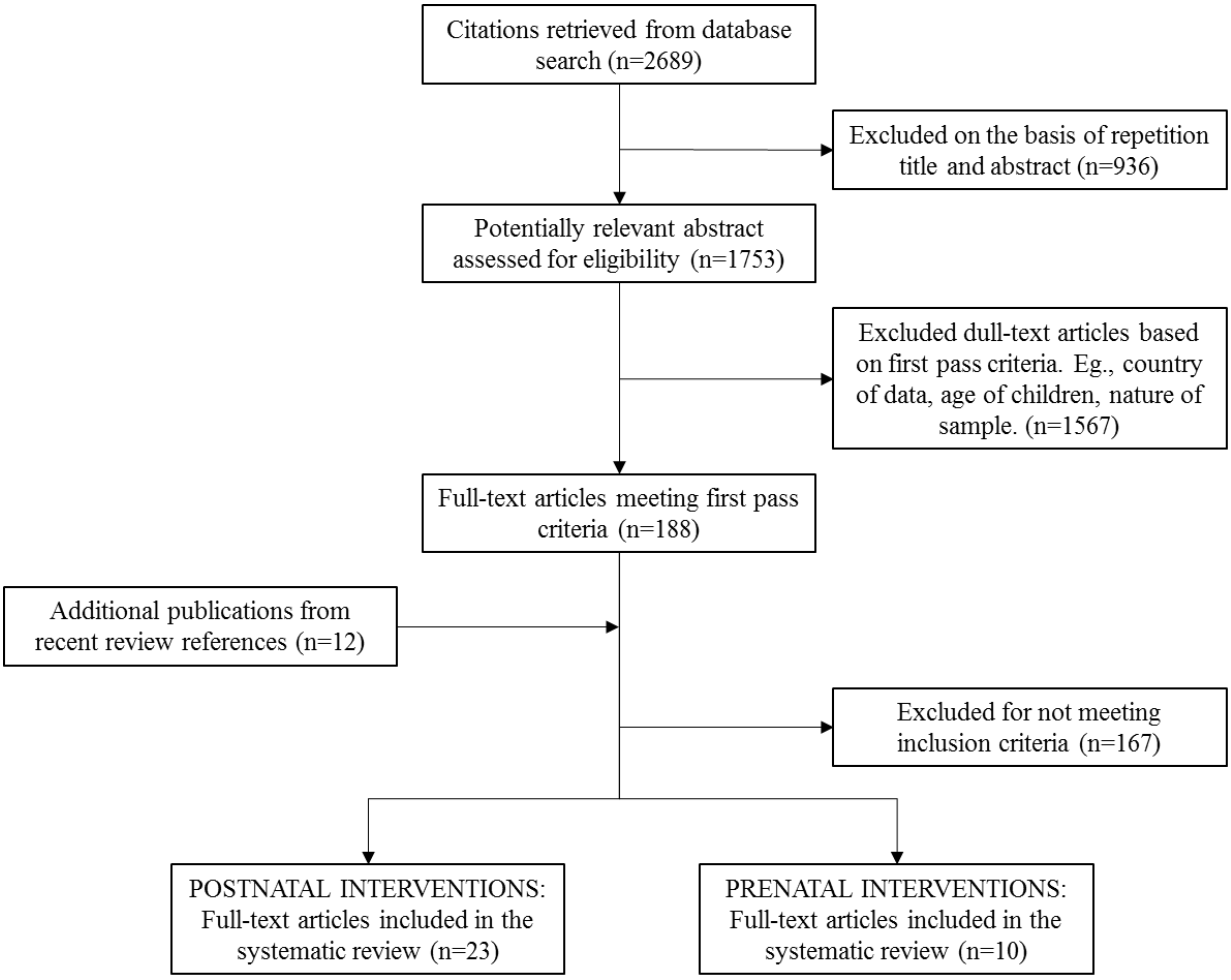
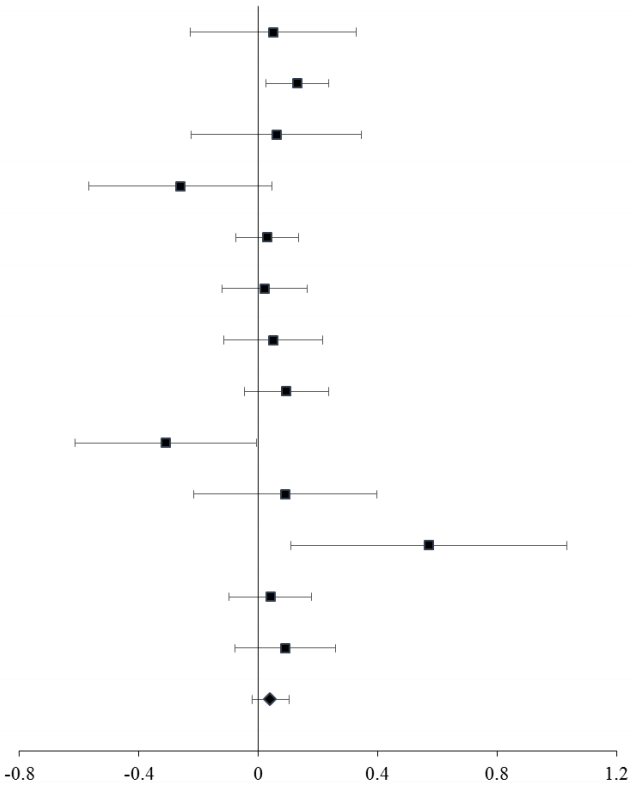


Figure 3.2: Forest plot for of mental development effect sizes for prenatal interventions

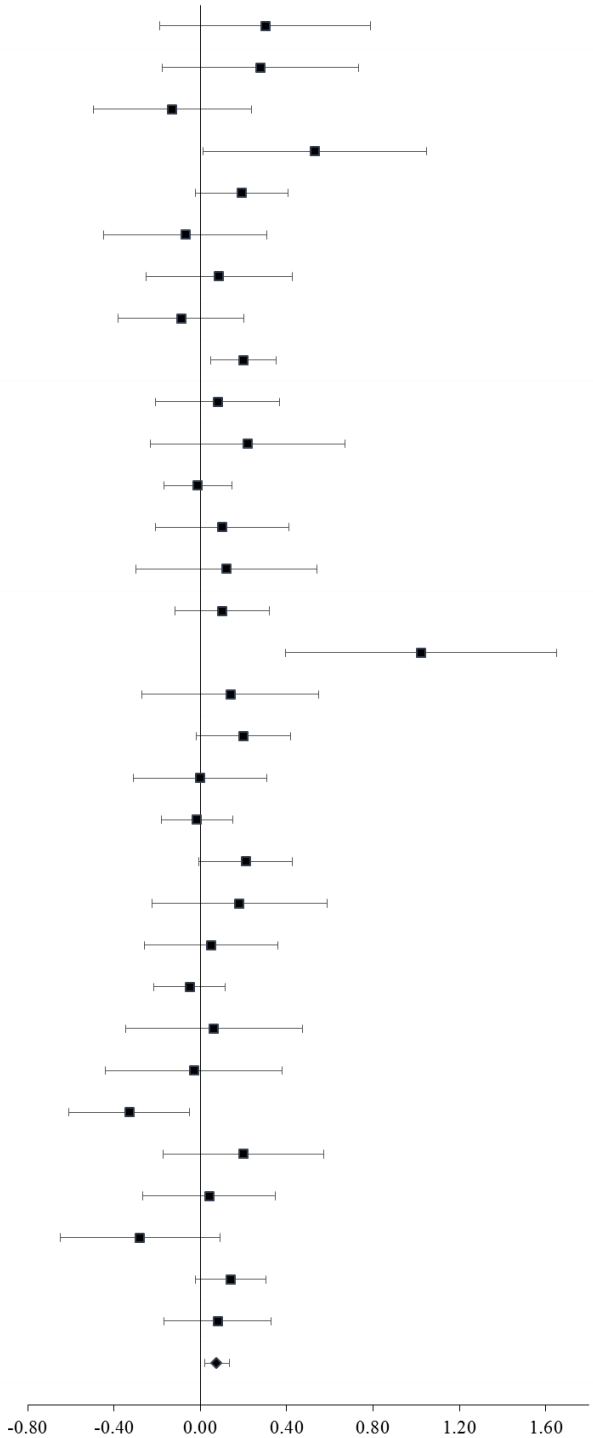
Author (year)	Country	Intervention	Weight (%)
Joos (1983)	Taiwan	Energy+protein	3.3
Tofail (2006)	Bangladesh	Omega-3 fatty acid	4.1
Schmidt (2004)	Indonesia	MMN	3.1
McGrath (2006)	Tanzania	MMN	2.7
Tofail (2008)	Bangladesh	MMN	23.3
Li (2009)	China	MMN	12.6
Chang (2013)	China	MMN	9.3
Hanieh (2013)	Vietnam	MMN	12.7
Hamadani (2002)	Bangladesh	Zn	2.7
McGrath (2006)	Tanzania	Vitamin A	2.7
Thilly (1980)	DR Congo	Iodine	1.2
Li (2009)	China	Fe/FA	13.4
Chang (2013)	China	Fe/FA	8.9
Overall Effect			100
Random Effects Model (I^2=22.4%)			



Note: MMN (multiple micronutrient); Zn (zinc); Fe (iron); FA (folic acid)

Figure 3.3: Forest plot for of mental development effect sizes for postnatal interventions

Author (year)	Country	Intervention	Weight (%)
Grantham-McGregor (1991)	Jamaica	Energy+protein	0.9
Politt (2000)	Indonesia	MMN+energy	1.0
Rosado (2011)	Mexico	MMN+energy+protein	1.6
Gurnida (2012)	Indonesia	Gangliosides	0.8
Manno (2012)	Zambia	MMN+energy	4.7
Phuka (2012)	Malawi	Energy	1.5
Nahar (2012)	Bangladesh	MMN+energy	1.9
Aboud (2011)	Bangladesh	MMN	2.6
Yousafzai (2014)	Pakistan	MMN	9.5
Singla (2014)	Bangladesh	MMN	2.6
Black (2004)	Bangladesh	MMN	1.1
Attanasio (2014)	Colombia	MMN	8.8
Siegel (2011)	Nepal	MMN	2.3
Black (2004)	Bangladesh	Fe/Zn	2.3
Lind (2004)	Indonesia	Fe/Zn	4.6
Idjradinata (1993)	Indonesia	Fe	0.5
Black (2004)	Bangladesh	Fe	0.5
Lind (2004)	Indonesia	Fe	4.6
Siegel (2011)	Nepal	Fe/FA	2.3
Surkan (2013)	Nepal	Fe/FA	8.0
Ashworth (1998)	Brazil	1mgZn	1.3
Ashworth (1998)	Brazil	5mgZn	1.3
Hamadani (2001)	Bangladesh	Zn	2.7
Castillo-Duran (2001)	Chile	Zn	1.6
Lind (2004)	Indonesia	Zn	4.6
Black (2004)	Bangladesh	Zn	1.3
Black (2004)	India	MMN+Zn	2.3
Gardner (2005)	Jamaica	Zn	1.6
Taneja (2005)	India	Zn	8.0
Siegel (2011)	Nepal	Zn	2.3
Surkan (2013)	Nepal	Zn	8.0
Colombo (2014)	Peru	Zn	3.5
Overall Effect			100



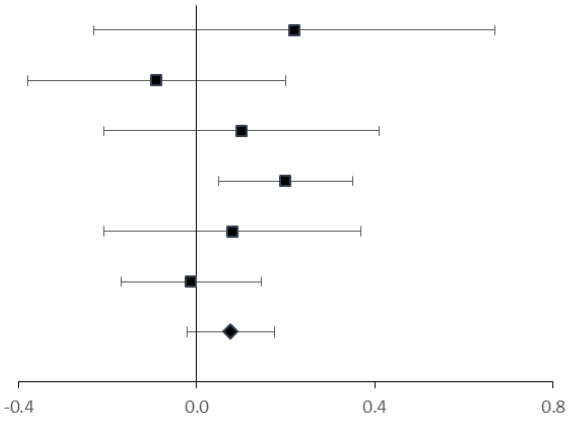
Random Effects Model (I^2=25.1%)

Note: MMN (multiple micronutrient); Zn (zinc); Fe (iron); FA (folic acid)

Figure 3.4: Forest plot for of mental development effect sizes for postnatal multiple micronutrient interventions

Author (year)	Country	Intervention	Weight (%)
Black (2004)	Bangladesh	MMN	4.0
Aboud (2011)	Bangladesh	MMN	9.6
Siegel (2011)	Nepal	MMN	8.4
Yousafzai (2014)	Pakistan	MMN	35.5
Singla (2014)	Bangladesh	MMN	9.7
Attanasio (2014)	Colombia	MMN	32.8
Overall Effect			100

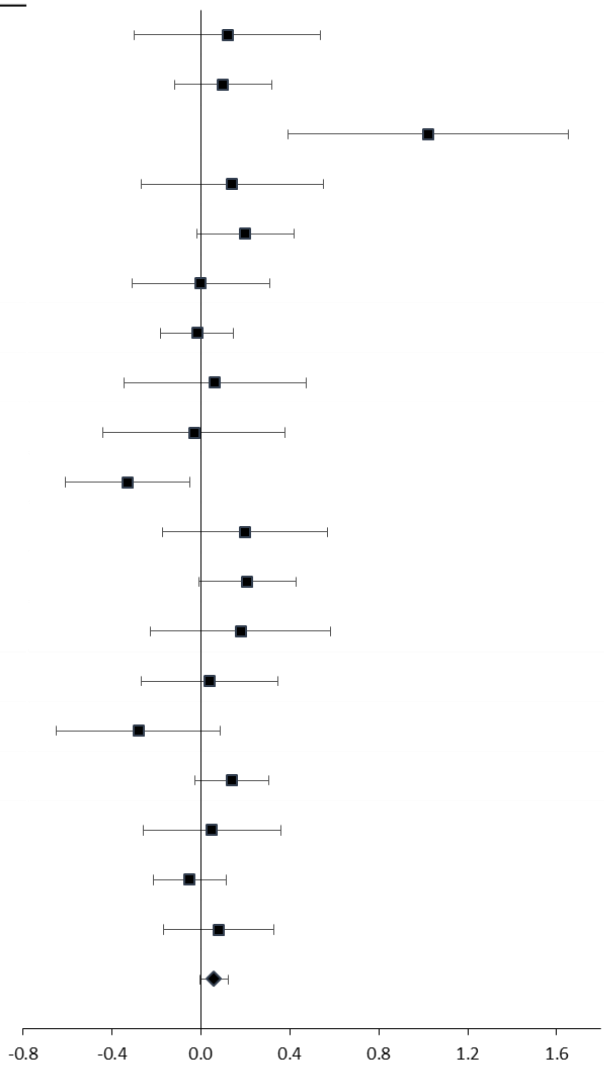
Random Effects Model (I^2=8.4%)



Note: MMN (multiple micronutrient)

Figure 3.5: Forest plot for of mental development effect sizes for postnatal single micronutrient interventions

Author (year)	Country	Intervention	Weight (%)
Black (2004)	Bangladesh	Fe/Zn	2.0
Lind (2004)	Indonesia	Fe/Zn	7.5
Idjradinata (1993)	Indonesia	Fe	0.9
Black (2004)	Bangladesh	Fe	2.1
Lind (2004)	Indonesia	Fe	7.5
Siegel (2011)	Nepal	Fe/FA	3.7
Surkan (2013)	Nepal	Fe/FA	13.1
Ashworth (1998)	Brazil	1mgZn	2.1
Ashworth (1998)	Brazil	5mgZn	2.1
Hamadani (2001)	Bangladesh	Zn	4.5
Castillo-Duran (2001)	Chile	Zn	2.6
Lind (2004)	Indonesia	Zn	7.5
Black (2004)	Bangladesh	Zn	2.2
Black (2004)	India	MMN+Zn	3.7
Gardner (2005)	Jamaica	Zn	2.6
Taneja (2005)	India	Zn	13.2
Siegel (2011)	Nepal	Zn	3.7
Surkan (2013)	Nepal	Zn	13.1
Colombo (2014)	Peru	Zn	5.7
Overall Effect			100



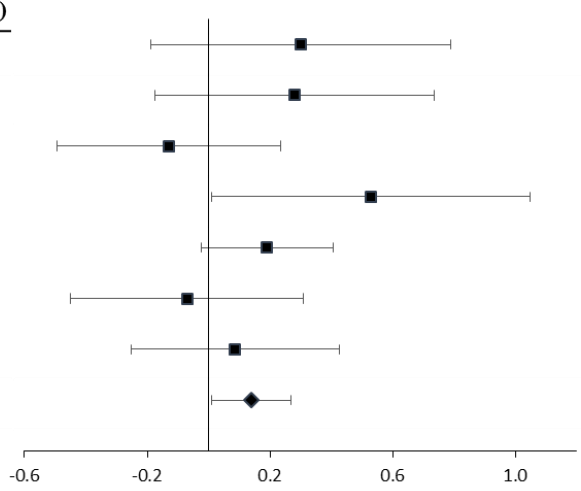
Random Effects Model (I^2=38.9%)

Note: MMN (multiple micronutrient); Zn (zinc); Fe (iron); FA (folic acid)

Figure 3.6: Forest plot for of mental development effect sizes for postnatal energy, protein, and fat interventions

Author (year)	Country	Intervention	Weight (%)
Grantham-McGregor (1991)	Jamaica	Energy+protein	7.3
Politt (2000)	Indonesia	MMN+energy	8.4
Rosado (2011)	Mexico	MMN+energy+protein	13.1
Gurnida (2012)	Indonesia	Gangliosides	6.4
Manno (2012)	Zambia	MMN+energy	37.7
Phuka (2012)	Malawi	Energy	12.1
Nahar (2012)	Bangladesh	MMN+energy	15.1
Overall Effect			100

Random Effects Model (I^2=8.1%)



Note: MMN (multiple micronutrient)

Figure 3.7: Funnel plot for postnatal interventions

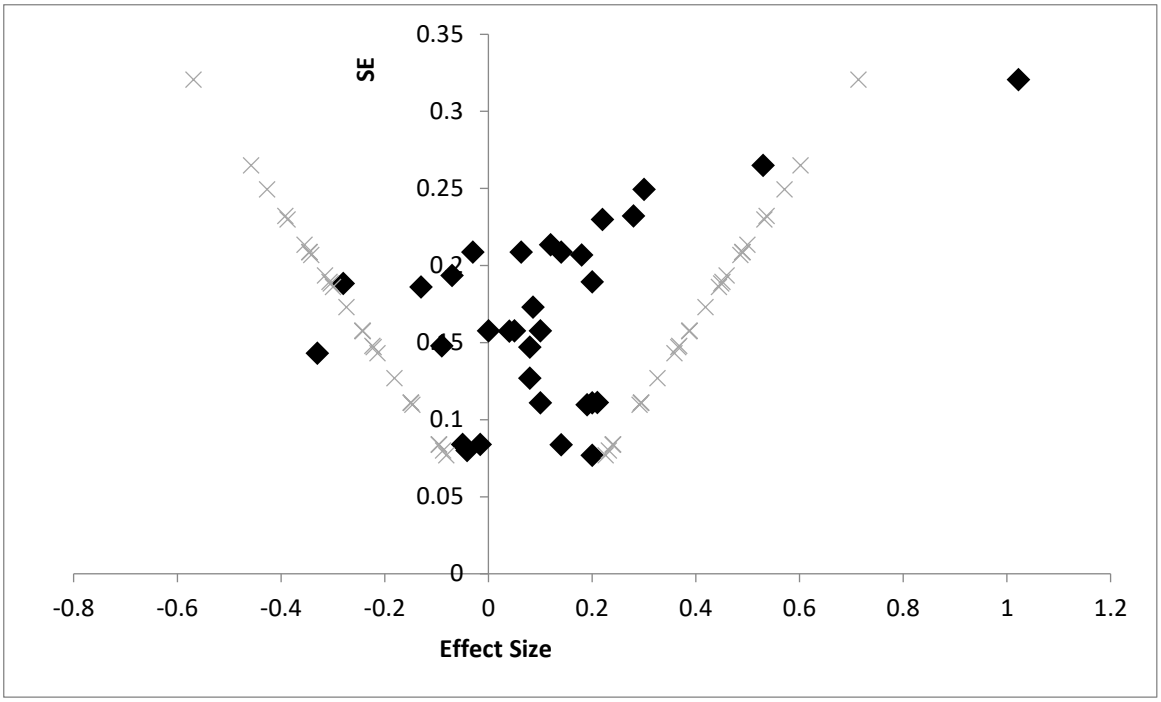
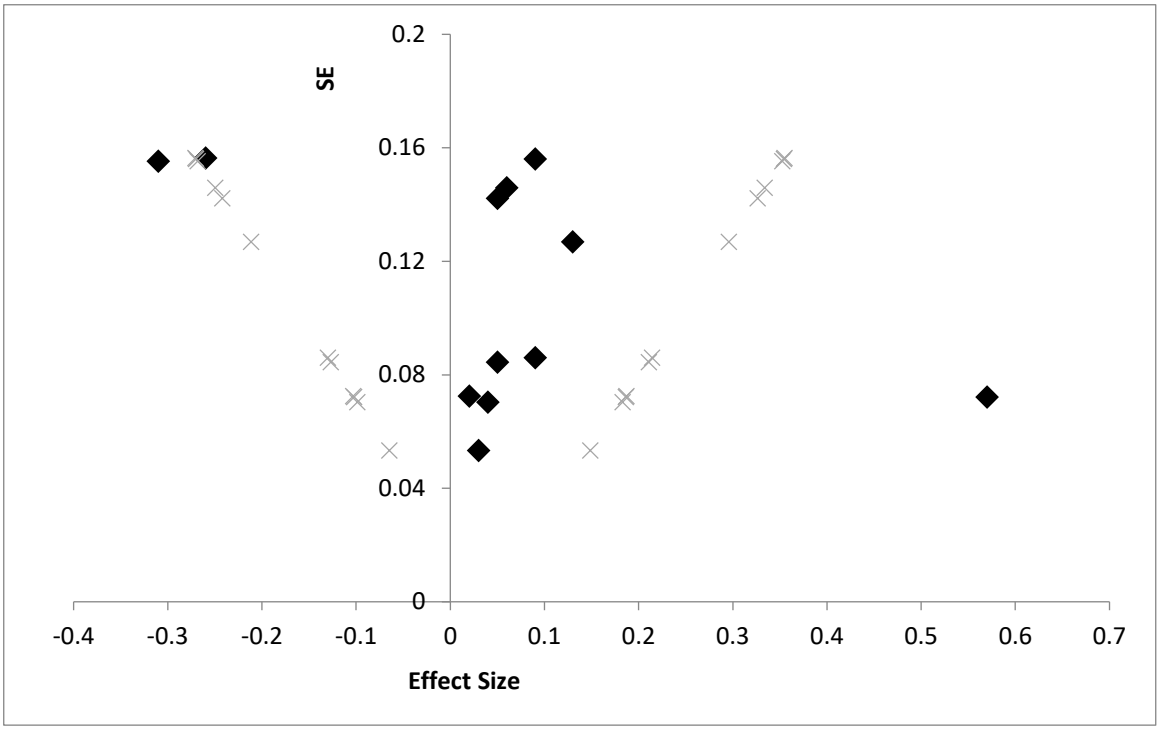


Figure 3.8: Funnel plot for prenatal interventions



3.8 Bridge statement 1

This meta-analysis of pre- and post-natal nutrition interventions in children under two years of age living in LMICs indicates a weak, yet significant, effect on mental development from postnatal interventions. Further, there is a non-significant trend toward greater benefit on mental development from interventions using macronutrients and multiple micronutrients as compared to single micronutrients. Few multiple micronutrient trials examined effects on mental development during this sensitive period and only one multiple micronutrient study included in this meta-analysis was adequately powered to detect an effect on mental development. Chapter 5 of this dissertation intends to address this gap by examining effects of home fortification with MNPs on mental development of children 6-18 months of age living in rural India. Our study is powered to detect and effect size of 0.1 or larger and targets a population with high risk of poverty and malnutrition.

Next, the meta-analysis indicates that most nutrition interventions in LMICs use general behavioral measures of child development, such as the BSID and the Griffiths, which may obscure the effects of nutrition interventions on specific cognitive functions which are developing rapidly during this stage. Inconclusive evidence from studies to date may be in part due to the use of insensitive measurement methods. Chapter 5 addresses this methodological limitation by examining the effects of home fortification with MNPs on two specific cognitive functions, memory and executive functions, that have been shown to be predictive of later intelligence, in addition to language, personal-social, cognitive, and motor development.

Lastly, the meta-analysis found that motor development effect size, but not HAZ, was a significant predictor of mental development effect size. We found that the majority of the literature did not report effects on mediators between nutrition and mental development. In particular, few interventions report on mediating pathways between the intervention and functional outcomes, such as

child development. Investigation of the mediating pathways to mental development, including stunting, illness, motor development and temperament, are needed to create a stronger evidence base for their impact on early mental development in resource-poor settings. Chapters 4 and 6 intend to address this gap. Chapter 4 examines nutritional, environmental, and social correlates of mental development in infants and young children in rural India, and goes further to examine mediators between dietary diversity and mental development scores. Measured mediators include LAZ, psychosocial stimulation, fine and gross motor development. Chapter 6 uses path analysis to examine how data fit to a conceptual framework for how nutrition affects mental development. Direct and indirect associations are examined between diet, hemoglobin, LAZ, motor development, stimulation, and an array of cognitive domains.

Chapter 4: A cross-sectional survey in rural Bihar, India indicates that nutritional status, diet and stimulation are associated with motor and mental development in young children

Leila M Larson, MPH,[1] Melissa F Young, PhD,[1,2] Usha Ramakrishnan, MS, PhD,[1,2] Amy Webb Girard, PhD,[1,2] Pankaj Verma, MBBS,[3], Indrajit Chaudhuri, MBA,[3] Sridhar Srikantiah, MD,[3] Reynaldo Martorell, PhD[1,2]

[1] Emory University, Nutrition and Health Sciences Program, Laney Graduate School, Atlanta, USA
[2] Emory University, Hubert Department of Global Health, Rollins School of Public Health, Atlanta, USA
[3] CARE India, Bihar, India

From Journal of Nutrition, Vol. 147, Issue 8, August 2017

Published online ahead of print June 2017

4.1 Abstract

Background: Many malnourished children in resource-poor settings fail to fulfill their developmental potential.

Objectives: The objectives of this analysis were to examine nutritional, psychosocial, environmental, and household correlates of child development in Bihar, and identify mediators between dietary diversity and mental development.

Design: Using two-stage cluster randomized sampling we surveyed 4360 households with children 6-18 months of age in West Champaran district, Bihar, India. We measured motor and mental development using the Developmental Milestones Checklist II. In a random subsample (n=2838), we measured anthropometry and hemoglobin. Cluster adjusted multiple linear regression analysis was used to examine associations between nutrition indicators and development scores. Sobel's test was used to assess significant mediators in the association between diet diversity and development scores. Analyses were stratified by children 6-11 months and 12-18 months.

Results: In all children, length-for-age z-score (LAZ), dietary diversity, and psychosocial stimulation were significant ($P<0.05$) correlates of motor [in children 6-11 months: LAZ $\beta=0.46$ (SE=0.08), dietary diversity $\beta=0.43$ (SE=0.09), stimulation $\beta=0.15$ (SE=0.04); in children 12-18 months: LAZ $\beta=0.73$ (SE=0.07), dietary diversity $\beta=0.30$ (SE=0.09), stimulation $\beta=0.31$ (SE=0.05)] and mental development scores [in children 6-11 months: LAZ $\beta=0.57$ (SE=0.10), dietary diversity $\beta=0.84$ (SE=0.13), stimulation $\beta=0.54$ (SE=0.07); in children 12-18 months: LAZ $\beta=0.54$ (SE=0.11), dietary diversity $\beta=0.40$ (SE=0.16), stimulation $\beta=0.62$ (SE=0.09)]. Stimulation, gross motor, and fine motor development were significant mediators in the relation between dietary diversity and mental development.

Conclusion: Strategies to improve dietary diversity and psychosocial stimulation could have important implications for child development of young North Indian children.

4.2 Introduction

Many children in low- and middle-income countries (LMICs) are exposed to malnutrition, poverty, poor health, and unstimulating environments, which detrimentally affect their development (1-3). It has been estimated 88 million children under five years of age in South Asia fail to fulfill their developmental potential (4); models using UNICEF's Early Child Development Index (ECDI) show that India has the largest estimated number of children 3-4 years of age (17.7 million children) with low cognitive and/or emotional development (3). Studies in resource-poor settings have examined the relation between nutrition and child development, many of which indicate that poor diet and nutritional status are associated with development (5, 6).

Brown and Pollitt (7) hypothesized that malnutrition affects child development through a number of mediators: child morbidity, energy level, motor development, and growth. Piecemeal evidence supports this model showing that children living in healthy environments are taller, have fewer illnesses, and are more likely to explore their environment through enhanced motor skills and activity; growth and exploration are positively associated with mental development (3, 8-10). Yet the mechanisms behind these relationships and their significance in Northern India remain unclear.

The Developmental Milestones Checklist-II (11) (DMC-II) is a parent report measure of infant and child motor and mental development, which has been used in parts of Sub-Saharan Africa. The DMC-II is a useful tool to measure child development in resource-poor settings; it can be administered by trained non-specialists, is simple to train on, and takes on average 15 minutes to complete. The objectives of the current analyses were to 1) establish the concurrent validity of the DMC-II as a measure of child development in the context of rural Bihar; 2) examine nutritional, psychosocial, environmental, and household correlates of motor and mental development; and 3) identify mediators of the relation between diet and mental development.

4.3 Participants and Methods

4.3.1 Study Setting

Bihar, one of the poorest states in India, has a female literacy rate of only 50% (12). Child malnutrition is an important public health problem in this northern state. According to the National Family Health Survey 2015-16 (NFHS-4), 48.3% of children are stunted, 20.8% are wasted, and 43.9% are underweight (12). Prevalence of anemia among children 6 months to 5 years of age, even though it has decreased 14.5 percentage points in the past ten years, is still at 63.5% (12).

4.3.2 Study Participants

This study includes children who participated in a baseline survey for a cluster randomized trial to study the effectiveness of home fortification with multiple micronutrient powders on anemia and child development. The study was conducted in rural West Champaran district in the state of Bihar. Four blocks (Bagaha-2, Chanpattiya, Lauriya, Mainatand) were purposefully chosen to include two blocks close to and two blocks far from district headquarters. Within each of these four blocks, health sub-centers (HSCs) which were prone to flooding and those prone to political difficulties were excluded. Using simple random sampling, a total of 70 HSCs were selected from those remaining. From September to October 2014, a baseline survey that included the DMC-II was administered in 4360 households with children 6-17.9 months of age (half 6-11.9 months of age and half 12-17.9 months) which were randomly selected from a household listing; a random subsample of 2838 households were selected for additional data collection on infant anthropometry and hemoglobin (**Supplemental Figure 4.1**).

4.3.3 Measurements

Child development was assessed using the DMC-II (11), a 75-item parent report of gross and fine motor, language, and personal-social development. Seven questions appropriate for children 6-18 months of age, taken from the Bayley's Scales of Infant and Toddler Development (BSID) (13) and validated (14), were added to assess cognitive development, a domain, which was not available from the DMC-II. Motor development includes the sum of scores from the gross and fine motor subscales; mental development includes the sum of scores from the language, personal-social, and cognitive subscales. Items were scored based on the duration for which the child had been performing the activity at the time of the interview as follows: 1 if the child had been performing this activity consistently for the past 4 weeks; 0.5 if performing the activity in the past 4 weeks but not consistently, or 0 if not yet performing the activity. This measure has been validated in Burkina Faso, Kenya, and Ghana (11, 15, 16). The Family Care Indicators (FCI), a 9-item parent-report measure, previously validated in South Asia (17), was used to assess stimulating caregiving.

A Wealth Index, using five categories, was calculated using principal component analysis with family assets, type of household, land ownership, and source of drinking water. A child dietary diversity score, minimum meal frequency value, and minimum acceptable diet value were created according to WHO guidelines (18). Food deprivation was assessed through mothers' report using the cross-culturally validated Household Hunger Scale (19). Households were classified as food deprived or not based on their responses to the 4-item Likert scale. Recent morbidity was measured as any fever, cough or diarrhea in the past two weeks reported by the caregiver. Thirty-two field investigators, trained and standardized, collected the household survey information, including the DMC-II.

Anthropometric measurements included weight, length, and mid-upper arm circumference (MUAC). Weight was assessed with the Seca 874 [Seca, Hamburg, Germany] and length with the Seca 417. Length-for-age, weight-for-length, and weight-for-age z-scores were calculated using the WHO

2006 child growth standards (20); z-scores less than -2 were used to define stunting, wasting, and underweight respectively; z-scores less than -3 were used to define severe stunting, severe wasting, and severe underweight. MUAC tapes (S0145620 MUAC, Child 11.5 Red/PAC-50) were used to measure MUAC.

Hemoglobin was measured with the HemoCue Hb 201+ Analyzar [HemoCue, Angelholm, Sweden]. Blood samples were taken using a heel prick from children 6-11 months of age, and a finger prick for children 12-18 months. Child anemia was defined as mild if 10g/dL≤ hemoglobin <11g/dL, moderate if 7g/dL≤ hemoglobin <10g/dL, and severe if hemoglobin <7g/dL (21). If a child was found to be severely anemic, they were referred to the nearest primary health center for consultation.

4.3.4 Ethical Considerations

A statement about study participation, which was approved during ethical review, was read to guardians and consent was obtained by thumb print or signature. Refusals were replaced. The study was approved by the Institutional Review Boards of the 3rd Futures Group, Delhi, India, and Emory University, Atlanta, USA and registered with the US National Institute of Health as a clinical trial (www.ClinicalTrials.gov; NCT02593136).

4.3.5 Quality Control

Field investigators had experience administering surveys; each had completed at least a secondary schooling. 32 field investigators and 10 supervisors were trained by specialists in nutrition and child development over a period of two weeks, which included field practice. Reliability of the field investigators' scores was established by examining the relationship between the field investigators' scores and those of an expert when assessing the same child, using five children (20, 22). The reliability measurements for the DMC-II gave an average kappa coefficient of 0.96. No single

kappa coefficient for any of the enumerators was below 0.70. Reliability measurements for weight, height, and MUAC yielded a Pearson's correlation coefficient between measurements of the investigators and expert of >0.92 and a coefficient of reliability of >0.80.

The survey was translated from English into Hindi and back-translated into English. The full survey, including the DMC-II was piloted on children from Bihar and adapted prior to starting the survey. The only adaptation necessary to the DMC-II was the order of questions in the personal-social subscale. During the survey, supervisors conducted 10% back-checks, which involved re-interviewing the caregiver on a random subset of questions and comparing results with the field investigators' results, and 10% spot-checks, which involved observing interviews.

4.3.6 Statistical Methods

We estimated a sample of 4340 children in order to have 90% power to detect a 10% difference in behavior (IYCF practices) assuming a baseline prevalence of 50%. A smaller sample size (N=2800) was estimated for hemoglobin measurements to detect a 12% reduction in anemia prevalence allowing for age stratification (children 6-11 and 12-18 months of age). For this analysis, this sample size gave us 90% power to detect an effect size of 0.10, using alpha=0.05, assuming 13 predictors in our multiple regression model.

Children with hemoglobin measurements below 4g/dL or above or equal to 18g/dL (23) (0.2%), or children with length-for-age z-scores <-6 or >6 (0.2%), weight-for-length z-scores <-5 or >5 (0.6%), or weight-for-age z-scores <-6 or >5 (0.5%) were omitted from the analysis (24).

Data were analyzed using SAS 9.4 (Cary, North Carolina, USA). The sample size was calculated based on the impact evaluation design. Clustering at the HSC level was accounted for using PROC SURVEY statements in SAS. Using anemia categories (no/mild/moderate/severe) rather than continuous hemoglobin concentration did not change the results. The regression and mediation

analyses were stratified by age (6-11.9 months and 12-17.9 months) because important motor and mental developmental milestones are achieved after 12 months, so variance due to age could overwhelm other predictors.

Cronbach's alpha for the total DMC-II score, and each subscale, was used to establish internal reliability, or how well questions measuring the same construct produce similar scores. Concurrent validity was examined through the sensitivity of the DMC-II to maternal education and child age using Pearson's correlation coefficients. Associations between socio-economic, nutritional, stimulation, environmental, and household factors and motor and mental development were first evaluated using univariate linear regression. A multiple regression model was then iteratively developed by retaining variables whose coefficients had p-values <0.05 and coefficients that did not show multi-collinearity based on a test of tolerance (>0.1) and variance inflation factor (<10). Standardized coefficients (with a mean of 0 and standard deviation of 1) were calculated for each variable retained in the multiple regression model. Mediation analyses were performed to examine potential mediators in the relation between dietary diversity and mental development of children 6-11 and 12-18 months of age. Potential mediators were chosen based on Brown and Pollitt's (7) conceptual framework of malnutrition and child development, and included growth, anemia, household stimulation, gross and fine motor development. Because recent illness was measured by parent report, over the past two weeks, it was not examined as a potential mediator in this model. Sobel's test was used to examine significant mediation (25).

4.4 Results

Household survey data and child development measures were collected from 4360 households. Anthropometric and hemoglobin measurements were obtained from 2838 children. Only two households refused the survey; four children refused hemoglobin measurements.

The majority of children had a low dietary diversity score (80%), many had morbidity in the past two weeks (76%), and 72% of children were anemic, 33% stunted (12% severely stunted), and 27% wasted (7% severely wasted) (**Table 4.1**). Almost all children (99%) were ever breastfed, with 95% still breastfeeding; however, only 39% of families practiced timely introduction of complementary foods at 6 months of age and 34% failed to feed the recommended number of meals per day.

4.4.1 Concurrent validity

The intra-cluster (HSC) correlation coefficient for the DMC-II score was 0.025. Internal reliability estimates were all acceptable, with Cronbach's alpha of 0.94 for the total score, 0.92 for motor, 0.79 for language, 0.82 for personal-social, and 0.67 for cognitive subscales. Each subscale was significantly correlated with the others using Pearson's correlation coefficient. Gross motor, fine motor, language, and personal-social development scores correlated with each other with coefficients ranging from 0.58 to 0.67. The cognitive subscale had correlation coefficients of 0.51 to 0.53 with gross motor, fine motor, and language scores, and 0.64 with personal-social scores.

The sensitivity of the DMC-II was evaluated for children of mothers with any education vs. no education. Children of mothers with no education scored consistently lower than children of mothers with any education: mean (95% CI) score of 40.0 (95% CI: 39.4, 40.7) vs. 42.3 (95% CI: 41.6, 43.0); $p<0.001$). Results were similar for each subscale with an effect size of 0.13 (95% CI: 0.07, 0.19) for motor, 0.20 (95% CI: 0.14, 0.26) for language, 0.18 (95% CI: 0.12, 0.24) for personal-social, and 0.27 (95% CI: 0.21, 0.33) for cognitive development.

The DMC-II's sensitivity to age was examined by correlating scores by child age in months. Correlations were: overall scores ($r=0.72$, $p<0.001$), motor ($r=0.73$, $p<0.001$), language ($r=0.59$, $p<0.001$), personal-social ($r=0.57$, $p<0.001$), and cognitive ($r=0.43$, $p<0.001$) development scores.

4.4.2 Child development and its correlates

Mean gross motor scores were 10.7 (95% CI: 10.5, 10.8) out of 22; mean fine motor scores were 6.5 (95% CI: 6.4, 6.6) out of 10. The total mental development score, the sum of language, personal-social and cognitive, was 23.8 (95%CI: 23.4, 24.2) out of 50. Mean scores broken down by age group for each mental development subscale are presented in Table 4.1.

Among children 6-11 months, multiple regression analyses indicate that motor development was significantly and positively associated with child age, LAZ, dietary diversity, WLZ and household stimulation but negatively associated with household food deprivation (**Table 4.2**). In children 12-18 months, motor development was significantly and positively associated with age, LAZ, WLZ, household stimulation and dietary diversity, but negatively associated with female sex and caste (Table 4.2).

Multiple regression analyses in the younger group show that mental development scores were positively and significantly associated with LAZ, dietary diversity and household stimulation and maternal education and negatively associated with being food deprived (**Table 4.3**). In the older group, mental development was similarly associated with age, LAZ, household stimulation, dietary diversity, household food deprivation and maternal education, as well as WLZ (Table 4.3).

4.4.3 Mediation between dietary diversity and mental development

Mediation analyses demonstrated that in both age groups, gross motor, and fine motor development were significant mediators of the relation between dietary diversity and mental development; household stimulation was a significant mediator in the older age group only (**Figures 4.1 and 4.2, Supplemental Table 4.1**). The results show a direct association between dietary diversity and mental development, with every addition of one diet group associated with a mean increase of 0.82 and 0.61 points in mental development score for children 6-11 months and 12-18 months respectively.

The coefficients for the indirect associations between dietary diversity and mental development through gross motor, fine motor, and household stimulation are displayed in Figures 4.1 and 4.2. When mental development was separated into language, and personal-social and cognitive development, similar results were obtained.

4.5 Discussion

Our contributions to knowledge about nutrition and child development in LMICs include 1) establishing the sensitivity of the DMC-II to child age and maternal education in the context of Northern India in children 6-18 months of age, 2) determining that LAZ, dietary diversity, and household stimulation are important correlates of motor and mental development, and 3) identifying household stimulation, gross, and fine motor development as significant mediators in the relation between dietary diversity and mental development.

The validity of the DMC-II in the context of rural Northern India was established by its sensitivity to maternal education and child age. Effect sizes for motor and personal-social subscale scores by maternal education are small but significant and replicate previous findings in Burkina Faso (11). The cognitive subscale that we added has also been examined in Ghana with similar internal and external validity results (14). Cognitive scores were strongly correlated with personal-social developments scores (measuring reaction to others, recognition of others, play, dressing, eating and drinking, and toilet training), suggesting that they measure abilities that develop concurrently and, in addition to language, contribute to a coherent score of mental development.

We hypothesized that psychosocial stimulation, growth, and nutritional factors were important correlates of child development. We found that household stimulation is a strong correlate of mental development and less so for motor development, consistent with other literature showing that a responsive and stimulating environment creates engaging situations for children to development their

cognitive, language, and social abilities (5, 26). LAZ was a more important correlate for development than WLZ. Low LAZ has repeatedly been associated with reduced motor and mental skills (4, 27) such that it is often used as a proxy of child development (4). A meta-analysis of data from 29 LMICs also determined that LAZ was significantly associated with cognitive abilities, age of walking, and motor skills (28). Our results show that dietary diversity is a more important correlate of development than food deprivation, which defines severe household nutritional stress. After adjusting for other significant correlates, food deprivation remains independently associated with development, and ours is the first study to document this in a LMIC setting. While food deprivation may indirectly affect motor and mental development through undernutrition and illness (29), it may also be detrimental to maternal mental health (30, 31) and impact the level of stimulation, care, and nutrition received by a child (32). Recent morbidity, anemia and distal factors, such as household wealth, and paternal education, were correlates of development when controlling for child age only but were no longer significant in the adjusted models. This could be due to their strong correlation with LAZ, dietary factors, and household stimulation (33-37).

The specific mechanism responsible for the relation between diet and development was explored through mediation analysis. Low dietary diversity was common and is potentially modifiable through community-based nutrition programs which would enhance nutrition of children. The diet of young children in rural Bihar is monotonous, and greater diversity in foods eaten could improve overall nutrition and development. The mediation analysis indicates that stimulation in children 12-18 months, along with fine and gross motor development in children 6-18 months are mediators in the relation between dietary diversity and mental development. Dietary diversity could influence the amount of stimulation in the home through several mechanisms: first, a child's diet is highly correlated with that of their mother (38) who is often the primary source of stimulation, and second, a mother who supplies a diverse diet to her child likely also supplies diversity of stimulation (39). Diet and stimulation are

more diverse in children 12-18 months and this may explain why stimulation is a significant mediator only in this older group. At this age, when a child starts walking and becoming increasingly active, the mother may become more aware of their child's stimulation needs and make materials more available. The significant mediation through motor skills demonstrated in this analysis may occur in a number of ways. Dietary diversity could build muscle through increased nutrients, including iron and animal-source foods, which in turn contribute to improved physical activity, initiative, leadership and social behaviors (40, 41). The resulting motor skills allow children to provide their own stimulation leading to the development of mental abilities (42). A more active child is also more likely to receive attention, be spoken to, and be heard by parents and others (39). Further, many personal-social and cognitive skills require fine motor coordination (e.g., putting on clothes, re-arranging small objects). Lastly, a child with more advanced motor skills may appear more mature and may be given more sophisticated stimulation (7). Previous work shows that nutrition can increase motor abilities and thereby children's interaction and exploration of their environment (7-9, 43), thus enhancing their mental development particularly when their experiences are mentally challenging (8). This is one of the first studies to show that all three aspects are connected.

The mediation analysis in this paper builds on previous work that established a framework linking nutrition and development (7, 43). However, the directionality of these relationships are hypothetical and the cross-sectional nature of this study does not allow for inferences of causality. For instance, greater fine motor skills could lead to more self-feeding, making the child appear more mature and ready for a more diverse diet.

Limitations of this analysis include the use of a parent-report measure of child development. Some bias could be introduced if mothers who recall certain motor skills are better at recalling mental abilities, or if mothers who are more involved in the development of their child are better able to recall activities and abilities. A more detailed examination of morbidity would be important in examining the

mechanisms linking diet and child development in future studies, for instance through an account over a longer period, and obtaining data on total number of days sick and severity of the illness. Lastly, the survey was performed in September and October, which are harvest months in Bihar. If performed during a less plentiful time, relationships between development and WLZ or morbidity may be different.

Despite these limitations, this analysis reveals important correlates of motor and mental development in young children. With the caveat that the study areas excluded those prone to flooding and political difficulties and therefore exclude areas that are potentially economically worse off, these findings could be generalizable to other parts of rural India with similar nutritional and economic indicators as Bihar. State programs in India that work on improving nutrition in early life, such as the National Nutrition Mission could impact child development by focusing on diversification of complementary foods. The mediation models extend the current framework for nutrition and child development (7, 43) by identifying both fine and gross motor abilities as significant mediators in the relation between diet and mental development and by identifying other nutritional indicators that drive the development of mental abilities in children 6 to 18 months of age. Further research examining a path analysis of the full theoretical model may help elucidate the indirect as well as direct pathways between nutrition and mental development.

Malnutrition is an important problem in LMICs with detrimental effects on child development. Our findings suggest that nutrition programs that target diversification of diets can have important implications for mental development of young Indian children, through their benefits on household stimulation and motor skills.

4.6 Acknowledgements

We have no conflicts of interest relevant to this article to disclose. Funding support provided by a Bill and Melinda Gates Foundation grant through a subcontract with CARE India. We wish to thank Rukshan Mehta and Priya Kekre for their contribution to the coordination of the study and data collection. Also, we wish to thank our collaborators, CARE India, for their support in the design and implementation of the study, as well as the women and children who participated in this study. Finally, we thank the Laney Graduate School at Emory University for funding Leila Larson while she pursues her PhD. The authors' responsibilities were as follows: LML designed the child development component of the study, supervised data collection, analyzed the data, and drafted the initial manuscript; MFY, UR, AWG, PV, IC, SS, and RM contributed to the design of the study, supervised data collection, and critically reviewed the manuscript. SS and RM secured funding for the study.

4.7 Chapter 4 references

1. Black MM, Hurley KM. Early child development programmes: further evidence for action. Lancet Glob Health 2016;4(8):e505-6. doi: 10.1016/s2214-109x(16)30149-8.
2. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P, et al. Every Newborn: progress, priorities, and potential beyond survival. Lancet 2014;384(9938):189-205. doi: 10.1016/s0140-6736(14)60496-7.
3. McCoy DC, Peet ED, Ezzati M, Danaei G, Black MM, Sudfeld CR, Fawzi W, Fink G. Early Childhood Developmental Status in Low- and Middle-Income Countries: National, Regional, and Global Prevalence Estimates Using Predictive Modeling. PLoS medicine 2016;13(6):e1002034. doi: 10.1371/journal.pmed.1002034.
4. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369(9555):60-70. doi: 10.1016/s0140-6736(07)60032-4.
5. Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol 2015;66:433-57. doi: 10.1146/annurev-psych-010814-015128.
6. Iannotti L, Jean Louis Dulience S, Wolff P, Cox K, Lesorogol C, Kohl P. Nutrition factors predict earlier acquisition of motor and language milestones among young children in Haiti. Acta Paediatr 2016;105(9):e406-11. doi: 10.1111/apa.13483.
7. Brown JL, Pollitt E. Malnutrition, poverty and intellectual development. Scientific American 1996;274(2):38-43.
8. Aburto NJ, Ramirez-Zea M, Neufeld LM, Flores-Ayala R. The effect of nutritional supplementation on physical activity and exploratory behavior of Mexican infants aged 8-12 months. European journal of clinical nutrition 2010;64(6):644-51. doi: 10.1038/ejcn.2010.52.
9. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children under-two in low- and middle-income countries. Maternal & child nutrition 2017;13(1). doi: 10.1111/mcn.12229.
10. MacIntyre J, McTaggart J, Guerrant RL, Goldfarb DM. Early childhood diarrhoeal diseases and cognition: are we missing the rest of the iceberg? Paediatr Int Child Health 2014;34(4):295-307. doi: 10.1179/2046905514y.0000000141.
11. Prado EL, Abubakar AA, Abbeddou S, Jimenez EY, Some JW, Ouedraogo JB. Extending the Developmental Milestones Checklist for use in a different context in Sub-Saharan Africa. Acta paediatrica (Oslo, Norway : 1992) 2014;103(4):447-54. doi: 10.1111/apa.12540.
12. International Institute of Population Sciences. India National Family Health Survey (NFHS-4), 2015-2016. Mumbai. http://rchiips.org/NFHS/pdf/NFHS4/BR_FactSheet.pdf: International Institute for Population Sciences, 2016.
13. Bayley N. Bayley Scales of Infant Development Manual. Third ed. Antonio, TX: The Psychological Corporation, 2006.
14. Ahun M. Maternal and child health and development in rural Ghana. Department of Psychology. Montreal, Quebec: McGill University, 2015.
15. Abubakar A, Holding P, Van de Vijver F, Bomu G, Van Baar A. Developmental monitoring using caregiver reports in a resource-limited setting: the case of Kilifi, Kenya. Acta paediatrica (Oslo, Norway : 1992) 2010;99(2):291-7. doi: 10.1111/j.1651-2227.2009.01561.x.
16. Ahun MN, Aboud FE, Aryeetey R, Colecraft E, Marquis GS. Maternal and child health, nutrition and development in rural Ghana. Canadian Conference on Global Health. Montreal, 2015.

17. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. Journal of health, population, and nutrition 2010;28(1):23.
18. WHO. Indicators for assessing infant and young child feeding practices: part 1: definitions. Geneva. http://apps.who.int/iris/bitstream/10665/43895/1/9789241596664_eng.pdf: World Health Organization, 2008.
19. Ballard T, Coates J, Swindale A, Deitchler M. Household hunger scale: indicator definition and measurement guide. Food and Nutrition Technical Assistance II Project, FHI 2011;360.
20. de Onis M, Onyango AW, Van den Broeck J, Chumlea WC, Martorell R. Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference. Food and nutrition bulletin 2004;25(1 Suppl):S27-36.
21. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva. http://www.who.int/vmnis/indicators/haemoglobin.pdf: World Health Organization, 2011.
22. Fernald LCH, Kariger P, Engle P, Raikes A. Examining early child development in low-income countries. Washington DC: The World Bank 2009.
23. Sullivan KM, Mei Z, Grummer-Strawn L, Parvanta I. Haemoglobin adjustments to define anaemia. Trop Med Int Health 2008;13(10):1267-71. doi: 10.1111/j.1365-3156.2008.02143.x.
24. WHO. WHO Child Growth Standards SAS igrowup package. Geneva. http://www.who.int/childgrowth/software/readme_sas.pdf: World Health Organization, 2011.
25. Sobel M. Asymptotic confidence intervals for indirect effects in structural equations models. Edtion ed. In: Leinhart S, ed. Sociological methodology San Francisco: Jossey-Bass, 1982:290–312.
26. Aboud FE, Yousafzai AK. Very Early Childhood Development. Edtion ed. In: Black RE, Laxminarayan R, Temmerman M, Walker N, eds. Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, Third Edition (Volume 2). Washington DC: 2016 International Bank for Reconstruction and Development / The World Bank., 2016.
27. Walker SP, Chang SM, Vera-Hernandez M, Grantham-McGregor S. Early childhood stimulation benefits adult competence and reduces violent behavior. Pediatrics 2011;127(5):849-57. doi: 10.1542/peds.2010-2231.
28. Sudfeld CR, McCoy DC, Danaei G, Fink G, Ezzati M, Andrews KG, Fawzi WW. Linear growth and child development in low- and middle-income countries: a meta-analysis. Pediatrics 2015;135(5):e1266-75. doi: 10.1542/peds.2014-3111.
29. Hadley C, Tessema F, Muluneh AT. Household food insecurity and caregiver distress: equal threats to child nutritional status? Am J Hum Biol 2012;24(2):149-57. doi: 10.1002/ajhb.22200.
30. Hadley C, Stevenson EG, Tadesse Y, Belachew T. Rapidly rising food prices and the experience of food insecurity in urban Ethiopia: impacts on health and well-being. Soc Sci Med 2012;75(12):2412-9. doi: 10.1016/j.socscimed.2012.09.018.
31. Jebena MG, Lindstrom D, Belachew T, Hadley C, Lachat C, Verstraeten R, De Cock N, Kolsteren P. Food Insecurity and Common Mental Disorders among Ethiopian Youth: Structural Equation Modeling. PLoS One 2016;11(11):e0165931. doi: 10.1371/journal.pone.0165931.
32. Liu Y, Kaaya S, Chai J, McCoy DC, Surkan PJ, Black MM, Sutter-Dallay AL, Verdoux H, Smith-Fawzi MC. Maternal depressive symptoms and early childhood cognitive development: a meta-analysis. Psychol Med 2016:1-10. doi: 10.1017/s003329171600283x.
33. Corsi DJ, Mejia-Guevara I, Subramanian SV. Risk factors for chronic undernutrition among children in India: Estimating relative importance, population attributable risk and fractions. Soc Sci Med 2016;157:165-85. doi: 10.1016/j.socscimed.2015.11.014.

34. Das JK, Salam RA, Imdad A, Bhutta ZA. Infant and Young Child Growth. Edtion ed. In: Black RE, Laxminarayan R, Temmerman M, Walker N, eds. Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, Third Edition (Volume 2). Washington DC: 2016 International Bank for Reconstruction and Development / The World Bank., 2016.
35. Kassa T, Meshesha B, Haji Y, Ebrahim J. Appropriate complementary feeding practices and associated factors among mothers of children age 6-23 months in Southern Ethiopia, 2015. BMC Pediatr 2016;16:131. doi: 10.1186/s12887-016-0675-x.
36. Keusch GT, Rosenberg IH, Denno DM, Duggan C, Guerrant RL, Lavery JV, Tarr PI, Ward HD, Black RE, Nataro JP, et al. Implications of acquired environmental enteric dysfunction for growth and stunting in infants and children living in low- and middle-income countries. Food Nutr Bull 2013;34(3):357-64.
37. Peterson KM, Buss J, Easley R, Yang Z, Korpe PS, Niu F, Ma JZ, Olortegui MP, Haque R, Kosek MN, et al. REG1B as a predictor of childhood stunting in Bangladesh and Peru. Am J Clin Nutr 2013;97(5):1129-33. doi: 10.3945/ajcn.112.048306.
38. Leroy JL, Olney D, Ruel M. Tubaramure, a Food-Assisted Integrated Health and Nutrition Program in Burundi, Increases Maternal and Child Hemoglobin Concentrations and Reduces Anemia: A Theory-Based Cluster-Randomized Controlled Intervention Trial. J Nutr 2016;146(8):1601-8. doi: 10.3945/jn.115.227462.
39. Aboud FE, Singla DR, Nahil MI, Borisova I. Effectiveness of a parenting program in Bangladesh to address early childhood health, growth and development. Social science & medicine (1982) 2013;97:250-8. doi: 10.1016/j.socscimed.2013.06.020.
40. Neumann CG, Jiang L, Weiss RE, Grillenberger M, Gewa CA, Siekmann JH, Murphy SP, Bwibo NO. Meat supplementation increases arm muscle area in Kenyan schoolchildren. Br J Nutr 2013;109(7):1230-40. doi: 10.1017/s0007114512003121.
41. Neumann CG, Murphy SP, Gewa C, Grillenberger M, Bwibo NO. Meat supplementation improves growth, cognitive, and behavioral outcomes in Kenyan children. The Journal of nutrition 2007;137(4):1119-23.
42. Adolph KE, Tamis-LeMonda CS. The Costs and Benefits of Development: The Transition From Crawling to Walking. Child Dev Perspect 2014;8(4):187-92. doi: 10.1111/cdep.12085.
43. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72(4):267-84. doi: 10.1111/nure.12102.

Table 4.1: Demographic and clinical characteristics of children 6-18 months of age[1]

		Children 6-11 months of age (N=2208)	Children 12-18 months of age (N=2152)
Child characteristics	Gender		
	Girls	49.7 (1096)	49.8 (1070)
Family characteristics	Religion		
	Hindu	79.1 (1745)	78.5 (1687)
	Muslim	20.9 (462)	21.5 (461)
	Mean maternal age (years)	25.0 ± 4.8	25.4 ± 4.7
	Mean paternal age (years)	29.2 ± 5.5	29.7 ± 6.1
	Maternal education		
	Any schooling	41.2 (909)	38.5 (828)
	Paternal education		
	Any schooling	63.8 (1403)	64.1 (1374)
Household characteristics	Mean number of preschool age children in the household	2.6 ± 1.6	2.7 ± 1.6
	Caste		
	Scheduled Caste	25.6 (564)	24.8 (533)
	Scheduled Tribe	8.1 (179)	8.4 (181)
	Other Backwards Caste	49.8 (1096)	51.2 (1098)
	Mean Family Care Indicators score (out of 13)	4.9 ± 2.2	5.4 ± 1.0
	Any food deprivation	9.8 (215)	9.1 (195)
Child nutrition indicators	Mean dietary diversity	2.5 ± 1.1	3.0 ± 1.0
	Score 4-7	13.4 (296)	27.4 (589)
	Starches	80.5 (1777)	96.1 (2068)
	Legumes and nuts	30.5 (674)	37.5 (807)
	Dairy	99.7 (2202)	99.7 (2146)
	Flesh foods	5.1 (112)	11.0 (237)
	Eggs	2.9 (64)	4.6 (98)
	Vitamin-A rich fruits and vegetables	11.2 (247)	21.7 (468)
	Other fruits and vegetables	15.6 (344)	30.4 (655)
	Minimum meal frequency achieved	60.8 (1315)	70.9 (1494)
	Minimum acceptable diet achieved	10.8 (239)	19.7 (423)
	Any recent child morbidity	76.9 (1698)	74.5 (1603)
	Fever	67.1 (1482)	64.8 (1393)
	Cough	56.5 (1246)	53.2 (1144)
	Diarrhea	11.0 (243)	12.7 (273)
	Anthropometry		
	Mean length-for-age z-score	-1.24 ± 1.30	-1.75 ± 1.30
	Mean weight-for-length z-score	-1.18 ± 1.15	-1.52 ± 1.11
	Mean weight-for-age z-score	-1.62 ± 1.13	-1.99 ± 1.10

	Mean mid-upper-arm-circumference	13.2 ± 1.1	13.1 ± 1.0
Anemia			
	Any (hemoglobin < 11g/dL)	70.5 (1002)	74.1 (1037)
	Mild (10 g/dL ≤ hemoglobin < 11 g/dL)	27.7 (393)	28.3 (396)
	Moderate (7 g/dL ≤ hemoglobin < 10 g/dL)	40.6 (577)	42.7 (598)
	Severe (hemoglobin < 7 g/dL)	2.3 (32)	3.1 (43)
Child development scores	Mean gross motor score (out of 22)	8.3 ± 2.8	13.1 ± 3.7
	Mean fine motor score (out of 10)	5.7 ± 1.8	7.3 ± 1.5
	Mean language score (out of 15)	3.1 ± 1.9	5.6 ± 2.5
	Mean personal-social score (out of 28)	13.8 ± 3.5	17.3 ± 3.3
	Mean cognitive score (out of 7)	3.4 ± 1.6	4.5 ± 1.4

[1]Values are mean ± SD or %(N). All estimates account for cluster-randomization by Health Sub-Center. Total N=4360 for all measurements (N=2208 for children 6-11 months of age, N=2152 for children 12-18 months of age) except for anthropometry and anemia, for which N=2838 (N=1432 for children 6-11 months of age, N=1406 for children 12-18 months of age). Minimum meal frequency is achieved if a breastfed child is fed at least three times or a non-breastfed child is fed at least four times the previous day. Minimum acceptable diet is achieved if a breastfed child is fed four or more food groups and achieved minimum meal frequency or a non-breastfed child received at least two milk feeds, is fed four or more foods groups and achieved minimum meal frequency the previous day. CI, confidence interval; SD, standard deviation.

Table 4.2: Association of child motor development score with child conditions for children 6-11 (left) and 12-18 (right) months of age[1]

	Children 6-11 months of age			**Children 12-18 months of age**		
	Univariate linear regression	Multiple linear regression		Univariate linear regression	Multiple linear regression	
Age (months)	1.47*** (1.37, 1.57)	1.42*** (1.31, 1.53)	0.59	1.25*** (1.13, 1.38)	1.18*** (1.04, 1.32)	0.45
Gender (male vs. female)	-0.22 (-0.48, 0.05)	-	-	-0.54** (-0.84, -0.24)	-0.72*** (-1.07, -0.37)	-0.08
Growth						
Length-for-age z-score	0.52*** (0.37, 0.67)	0.46*** (0.30, 0.61)	0.15	0.87*** (0.70, 1.04)	0.73*** (0.59, 0.88)	0.21
Weight-for-length z-score	0.27** (0.11, 0.43)	0.27** (0.11, 0.43)	0.08	0.66*** (0.44, 0.87)	0.50** (0.29, 0.71)	0.12
Anemia category	-0.09 (-0.30, 0.11)	-	-	0.34* (0.03, 0.64)	-	-
Other Nutritional Factors						
Food deprivation	-0.92*** (-1.36, -0.47)	-0.81** (-1.39, -0.22)	-0.06	-1.27*** (-1.85, -0.69)	-	-
Dietary diversity score	0.48*** (0.34, 0.63)	0.43*** (0.24, 0.61)	0.11	0.52*** (0.34, 0.70)	0.30** (0.11, 0.48)	0.07
Recent child morbidity	-0.50* (-0.89, -0.11)	-	-	-0.70** (-1.12, 0.28)	-	-
Household stimulation score	0.25*** (0.18, 0.33)	0.15** (0.07, 0.23)	0.08	0.38*** (0.28, 0.49)	0.31*** (0.20, 0.42)	0.16
Distal Factors						
Wealth index quintile	0.21** (0.10, 0.32)	-	-	0.45*** (0.31, 0.59)	-	-
Any maternal education	0.64** (0.33, 0.95)	-	-	1.10*** (0.79, 1.41)	-	-
Any paternal education	0.52*** (1.37, 1.56)	-	-	0.95*** (0.58, 1.32)	-	-
Caste	0.09 (-0.09, 0.26)	-	-	-0.23* (-0.45, -0.02)	-0.26** (-0.44, -0.09)	-0.07

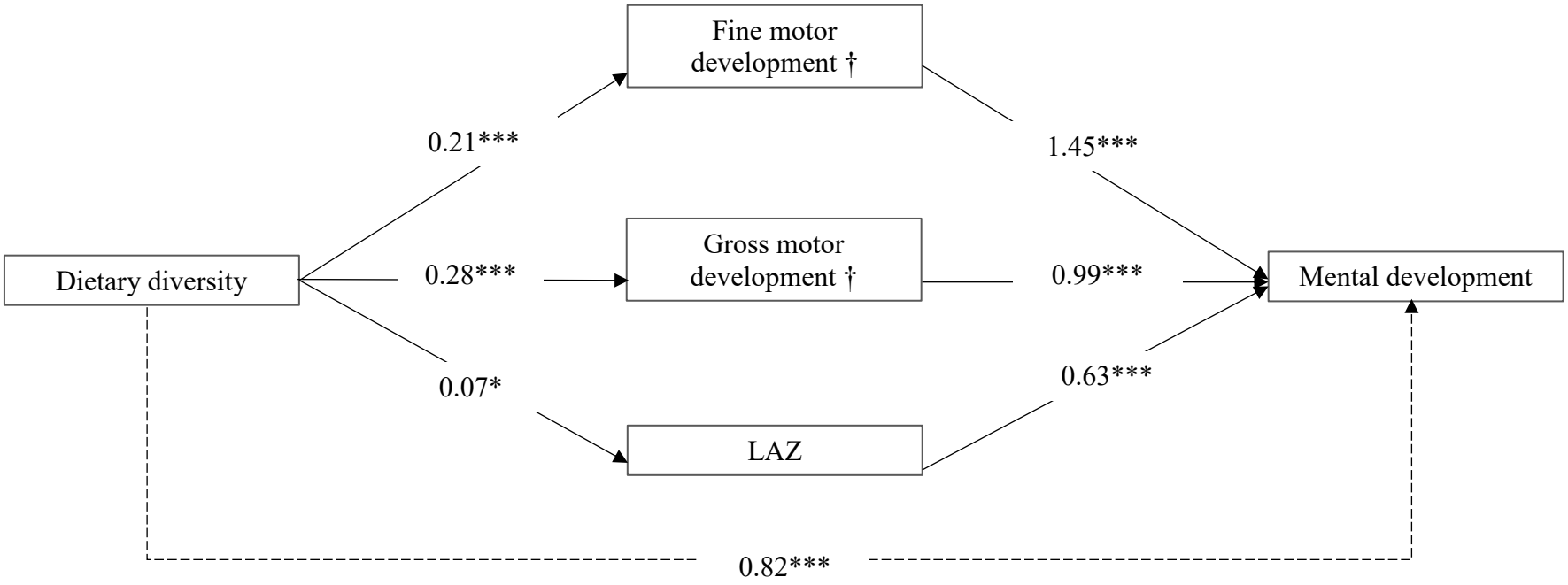
[1]Values are coefficients (95% CI) and standardized coefficients. All estimates account for cluster-randomization by Health Sub-Center and adjusted for age of child. Anemia categorized as moderate or severe (hemoglobin <10g/dL), mild (10g/dL≤ hemoglobin <11g/dL), and no anemia (hemoglobin ≥11g/dL). Recent child morbidity includes fever, cough, or diarrhea in the past two weeks. Multiple regression model iteratively developed with variables retained if P-value for their coefficient remained <0.05. Regression coefficient standardized with a mean of 0 and SD of 1. R^2=0.42 for the multiple regression model in children 6-11 months of age with motor development as the outcome. R^2=0.33 for the multiple regression model in children 12-18 months of age with motor development as the outcome. * p<0.05, ** p<0.01, *** p<0.001.

Table 4.3: Association of child mental development score with child conditions for children 6-11 (left) and 12-18 (right) months of age[1]

	Children 6-11 months of age			Children 12-18 months of age		
	Univariate linear regression	Multiple linear regression		Univariate linear regression	Multiple linear regression	
Age (months)	1.81*** (1.66, 1.97)	1.59*** (1.42, 1.76)	0.45	1.35*** (1.19, 1.51)	1.19*** (1.00, 1.37)	0.34
Gender (male vs. female)	-0.36 (-0.87, 0.15)	-	-	-0.19 (-0.51, 0.13)	-	-
Growth						
Length-for-age z-score	0.80*** (0.61, 1.00)	0.57*** (0.37, 0.76)	0.12	0.82*** (0.59, 1.05)	0.54*** (0.32, 0.75)	0.12
Weight-for-length z-score	0.30* (0.06, 0.53)	-	-	0.61*** (0.33, 0.89)	0.35** (0.11, 0.60)	0.07
Anemia category	-0.46 (-1.07, 0.15)	-	-	0.57 (-0.20, 1.33)	-	-
Other Nutritional Factors						
Food deprivation	-1.56*** (-2.29, -0.83)	-1.48** (-2.40, -0.56)	-0.07	-2.41*** (-3.38, -1.44)	-1.43** (-2.42, -0.44)	-0.07
Dietary diversity score	0.96*** (0.73, 1.19)	0.84*** (0.58, 1.10)	0.15	0.77*** (0.49, 1.06)	0.40* (0.07, 0.72)	0.07
Recent child morbidity	-0.03 (-0.59, 0.54)	-	-	-0.99** (-1.67, -0.31)	-	-
Household stimulation score	0.71*** (0.58, 0.83)	0.54*** (0.39, 0.69)	0.20	0.70*** (0.55, 0.85)	0.62*** (0.44, 0.81)	0.24
Distal Factors						
Wealth index quintile	0.62*** (0.44, 0.81)	-	-	0.72*** (0.50, 0.94)	-	-
Any maternal education	1.86*** (1.45, 2.27)	0.97** (0.40, 1.54)	0.08	1.61*** (1.15, 2.06)	0.64* (0.01, 1.27)	0.05
Any paternal education	1.27*** (0.83, 1.72)	-	-	1.32*** (0.78, 1.85)	-	-
Caste	0.18 (-0.07, 0.43)	-	-	-0.19 (-0.52, 0.14)	-	-

[1]Values are coefficients (95% CI) and standardized coefficients. All estimates account for cluster-randomization by Health Sub-Center and adjusted for age of child. Anemia categorized as moderate or severe (hemoglobin <10g/dL), mild (10g/dL≤ hemoglobin <11g/dL), and no anemia (hemoglobin ≥11g/dL). Recent child morbidity includes fever, cough, or diarrhea in the past two weeks. Multiple regression model iteratively developed with variables retained if P-value for their coefficient remained <0.05. Regression coefficient standardized with a mean of 0 and SD of 1. R^2=0.36 for the multiple regression model in children 6-11 months of age with mental development as the outcome. R^2=0.25 for the multiple regression model in children 12-18 months of age with mental development as the outcome. * p<0.05, ** p<0.01, *** p<0.001.

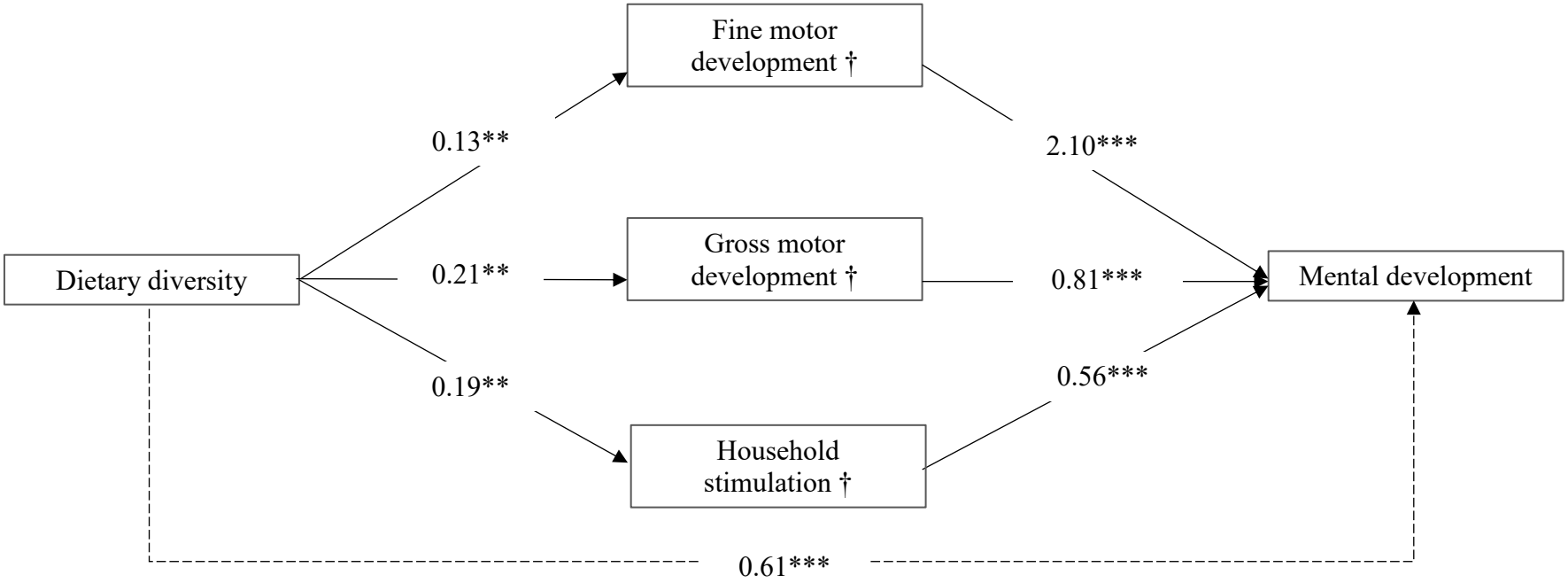
Figure 4.1: Mediation analysis between dietary diversity and mental development in children 6-11 months of age[1]



[1] Values are unstandardized coefficients. Covariates include age, household wealth, maternal education, paternal education, recent morbidity, caste, and food deprivation. All models account for cluster-randomization by Health Sub-Center. WLZ, household stimulation, and anemia not examined as potential mediators in children 6-11 months because not significantly associated with dietary diversity or the outcome. Solid arrows represent associations for each mediator separately. Associations between dietary diversity and mediators are adjusted for covariates; associations between mediators and mental development are adjusted for dietary diversity and covariates. Dashed arrow represents

association adjusting for covariates. LAZ, length-for-age z-score; WLZ, weight-for-length z-score. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. † significant mediator using Sobel test.

Figure 4.2: Mediation analysis between dietary diversity and mental development in children 12-18 months of age[1]



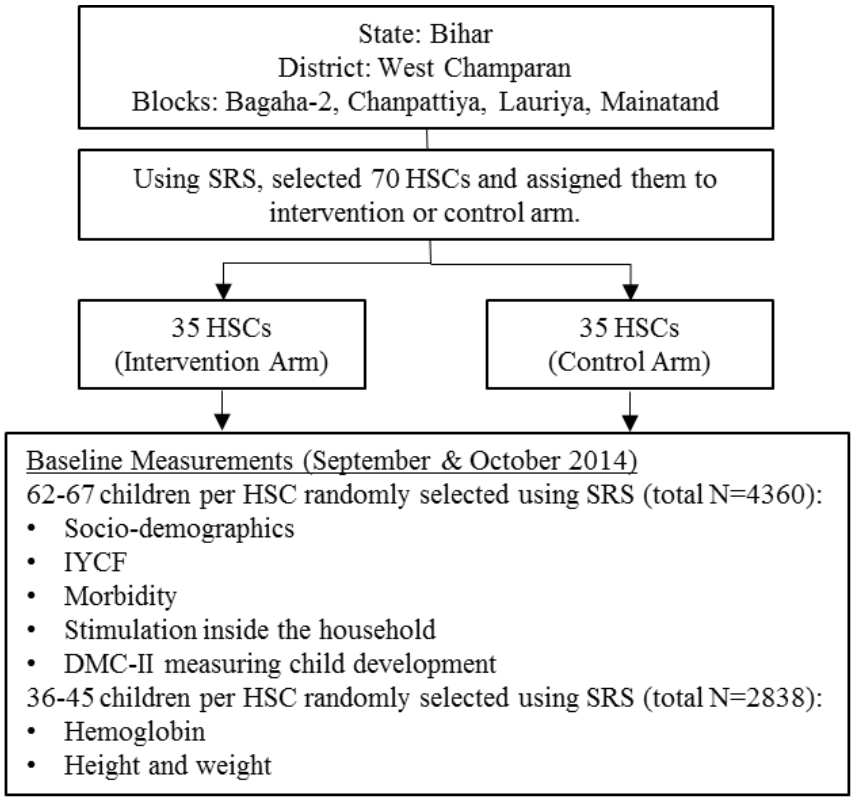
[1] Values are unstandardized coefficients. Covariates include age, household wealth, maternal education, paternal education, recent morbidity, caste, and food deprivation. All models account for cluster-randomization by Health Sub-Center. WLZ, LAZ, and anemia not examined as potential mediators in children 12-18 months because not significantly associated with dietary diversity or the outcome. Solid arrows represent associations for each mediator separately. Associations between dietary diversity and mediators are adjusted for covariates; associations between mediators and mental development are adjusted for dietary diversity and covariates. Dashed arrow represents association adjusting for covariates. LAZ, length-for-age z-score; WLZ, weight-for-length z-score. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. † significant mediator using Sobel test.

Supplemental Table 4.1: Association between dietary diversity and mental development score for children 6-11 and 12-18 months of age[1]

	Mental development score	
	6-11 months of age	**12-18 months of age**
Adjusted for clustering and child age	0.96*** (0.73, 1.19)	0.77*** (0.49, 1.06)
Adjusted for clustering and covariates	0.82*** (0.57, 1.06)	0.61*** (0.33, 0.89)
Adjusted for clustering, covariates, and LAZ	0.80*** (0.49, 1.11)	-
Adjusted for clustering, covariates, and household stimulation	-	0.50** (0.22, 0.78)†
Adjusted for clustering, covariates, and gross motor development	0.54*** (0.30, 0.77)†	0.44** (0.17, 0.71)†
Adjusted for clustering, covariates, and fine motor development	0.51*** (0.29, 0.73)†	0.34** (0.10, 0.57)†
Adjusted for clustering, covariates, and all potential mediators	0.43** (0.16, 0.71)	0.20 (-0.09, 0.49)

[1]Values are coefficients (95% CI). Covariates include age, household wealth, maternal education, paternal education, recent morbidity, caste, and food deprivation. All models account for cluster-randomization by Health Sub-Center. WLZ and anemia not examined as potential mediators in all children because not significantly associated with the outcome or with dietary diversity. LAZ not examined as a potential mediator in children 12-18 months, and household stimulation not examined as a potential mediator in children 6-11 months, because not significantly associated with dietary diversity. Values represent the estimate (95% confidence interval). LAZ, length-for-age z-score; WLZ, weight-for-length z-score. * $p<0.05$; ** $p<0.01$; *** $p<0.0001$. † significant mediator using Sobel test.

Supplemental Figure 4.1: Flowchart of study design and sampling strategy[1]



[1] Developmental Milestones Checklist-II (DMC-II); Front-line worker (FLW); Infant and Young Child Feeding (IYCF); Home fortification product (HFP); Health sub center (HSC); Simple random sampling (SRS)

4.8 Bridge statement 2

Chapter 4's initial contribution to the literature is to determine the concurrent validity of the DMC-II. By establishing the test's validity in the context of rural Bihar, we have the confidence to make conclusions based on the results observed in Chapters 4-6. Chapter 4 examined nutritional, psychosocial, environmental, and household correlates of child development in infants and young Bihari children. Cross-sectional associations using the baseline survey of a nutrition intervention indicated that LAZ, dietary diversity, and stimulation were significant correlates of motor and mental development scores. This confirmed previous literature on the importance of nutrition and stimulation on early child development. Food deprivation was also significantly associated with mental development, even after adjusting for other covariates, a somewhat novel and important finding for resource-poor settings. Further, the mediation analysis found that stimulation in children 12-18 months, and fine and gross motor development in children 6-18 months, were mediators between dietary diversity and mental development. This mediation analysis builds upon previous work and models to demonstrate how diet, motor development, stimulation, and mental development are related to one another. Establishing the correlates of mental development and mediators between diet and mental development is important in order to inform nutrition interventions and evaluations. They can indicate important modifiers and pathways through which a nutrition intervention affects child development. The manuscript in Chapter 5 examines the effect of home fortification with MNPs on motor and mental development of children 6-18 months of age living in rural Bihar, India. The analyses from Chapter 4 highlight variables which also need to be measured at endline because they are important for children's development.

Chapter 5: Effectiveness of a home fortification program with multiple micronutrients on infant and young child development: a cluster randomized trial in rural Bihar, India

Leila M Larson,[1] Melissa F Young,[1,2] Patricia J Bauer,[3] Rukshan Mehta,[1] Amy Webb Girard,[1,2] Usha Ramakrishnan,[1,2] Pankaj Verma,[4] Indrajit Chaudhuri,[4] Sridhar Srikantiah,[4] Reynaldo Martorell[1,2]

[1] Emory University, Nutrition and Health Sciences Program, Laney Graduate School, Atlanta, USA
[2] Emory University, Hubert Department of Global Health, Rollins School of Public Health, Atlanta, USA
[3] Emory University, Department of Psychology, Atlanta, USA
[4] CARE India, Bihar, India

5.1 Abstract

Background: Research demonstrates the importance of nutrition for brain and cognitive development in the early years of life.

Objectives: This study examined the impacts of home fortification with multiple micronutrient powders (MNPs) on motor and mental development, executive function, and memory of children 6-18 months of age living in West Champaran, Bihar.

Design: This two-arm cluster randomized effectiveness trial selected 70 health sub-centers to receive either MNPs and nutrition counseling (intervention) or nutrition counselling alone (control) for 12 months. Frontline health workers delivered the intervention to all households in study communities with a child 6-18 months of age. Data were collected using cross-sectional surveys at study baseline and endline by selecting households from intervention (N=2184 at baseline; 2170 at endline) and control (N=2176 at baseline; 2122 at endline) communities using a 2-stage cluster randomized sampling strategy. The Developmental Milestones Checklist-II was used to assess motor and mental development, the A-not-B test was used to assess executive function, and Elicited Imitation tasks were used to assess memory.

Results: Children in the intervention group had a significantly ($P<0.05$) larger improvement from baseline to endline compared to those in the control group on scores for motor and mental development (Cohen's d, motor=0.12, 95% CI: 0.03, 0.22; mental=0.15, 95% CI: 0.06, 0.25). We also found greater impacts of MNPs on motor and mental development for children from households with higher stimulation scores at baseline compared to those from households with lower stimulation scores at baseline (Cohen's d, motor=0.20 v. 0.09; mental=0.22 v. 0.14; P-interaction <0.05). No significant treatment differences were seen for executive function or memory.

Conclusion: Home fortification with MNPs through the existing health infrastructure in Bihar, India was effective in improving infant and child motor and mental development and should be considered in combination with other child development interventions such as stimulation.

Clinical Trial registry name and registration number: Home Fortification of Complementary Foods in Bihar India; NCT02593136

5.2 Introduction

Estimates indicate that 250 million children (43%) under five years of age do not fulfill their developmental potential in low- and middle-income countries (LMICs) (1). Poor development in early life has ongoing and long-term implications on school achievement and income and productivity (which tend to be lower), high fertility, and poor care for the next generation (2, 3). Proper nutrition especially during the first 1000 days can influence early development directly through brain development, and indirectly through reducing illness and improving growth, and enhancing the child's interactions with their environment (4).

Recent meta-analyses and reviews document the efficacy of early child nutrition interventions on development especially among children under two years of age from LMICs (5-7). Home fortification with multiple micronutrient powders (MNPs) is a simple intervention that requires caregivers to mix a sachet of micronutrients into their child's food prior to feeding. Although several studies have evaluated the efficacy of MNPs on young child development, few have studied the effectiveness of such programs when delivered using the existing government health infrastructure (8-10). Evidence from effectiveness trials is important if we are to transition to scale at a regional level (8).

Despite overall benefits of postnatal food and micronutrient interventions, trials have yielded inconsistent results on child development. One reason could be the outcome measurement. Global measures of child development, such as the Bayley's Scales of Infant and Child Development, which are typically used in nutrition studies in LMICs (6), can capture effects on motor and mental development broadly. Because of nutrients' specific functions in synaptic efficiency, myelination, and hippocampal development (11), micronutrient interventions may differentially affect specific cognitive functions which are masked in higher order assessment tools. Two such specific processes that underlie

early cognitive development (12-14) and are hypothesized to be related to nutritional status are executive function (15, 16) and memory (17-19).

The objectives of the current study were to examine the effectiveness of home fortification with MNPs on motor and mental development of children 6 to 18 months of age, and on executive function and declarative memory of children 12-18 months of age. We hypothesized that children from communities receiving the intervention would score higher on development, executive function, and memory tests than children from control communities.

5.3 Methods

This study was a collaboration between CARE India and Emory University. It was approved by the Institutional Review Boards of the 3rd Futures Group, Delhi, India, St John's Medical College & Hospital Institutional Ethics Committee, Bangalore, India, and Emory University, Atlanta, USA, and registered with the US National Institute of Health as a clinical trial (www.ClinicalTrials.gov; NCT02593136).

5.3.1 Setting

The government of Bihar, in partnership with the Bill and Melinda Gates Foundation and CARE India, launched the Integrated Family Health Initiative (IFHI) in 2011 to address pressing health challenges faced by its population. The IFHI identified childhood anemia (at 64% in children under five years in Bihar) (20) as one of the major public health priorities to be targeted. Based on evidence (21), home fortification with MNPs was identified as an innovative strategy to address this priority. The program was delivered by government front-line health workers with the support of CARE India,

the primary implementing partner of IFHI and Emory University that provided nutrition technical support. The goal of the study was to determine the effectiveness of the program in one district of Bihar prior to potential state-wide scaleup.

Extensive formative research was conducted between 2012 and 2014 to establish viability of the MNP product in this context (e.g., acceptability of the product, messaging, and visual messaging) (22). The current study was started following positive evidence for its acceptability by the community.

5.3.2 Study design and participants

We conducted a 12-month two-arm cluster randomized effectiveness trial in West Champaran district of Bihar, India, between January 2015 and December 2015 (**Figure 5.1**). In India, districts are subdivided into blocks (subdistricts). Four blocks were purposefully chosen to include two blocks close to and two blocks far from district headquarters. Within each of these four blocks, HSCs which were prone to flooding and political difficulties (n=35). Out of 135 health sub-center communities (HSCs), 70 were randomly assigned, using a simple randomization method with random number generator, to intervention or control communities (Figure 5.1); all families with children 6-18 months in these communities received complementary feeding counseling and intervention families additionally received the home fortification product, a multiple micronutrient powder labeled Jeevan Jyoti (the name means “the light of life” in Hindi, chosen by community members as part of formative research).

Two cross-sectional surveys of children 6 to 18 months of age were used to assess the change in outcomes. The baseline (N=4360) and endline (N=4292) surveys were conducted from August-September 2014 and from February-March 2016, respectively. Inclusion criteria for survey enrolment

were child's age above 6 months and below 18 months; half of whom were 6-11.9 months of age and the other half were 12-18 months of age.

For the baseline and endline evaluation, a household listing (list of eligible households) was performed prior to starting the survey. In HSCs with five or more AWCs, SRS was used to select five AWCs for which household listing was performed. Using the household listings, 31 children 6-11.9 months of age and 31 children 12-17.9 months of age from each HSC were chosen using SRS to be included in the household survey, which included questions on their child's mental and motor development. Refusals for the household survey were replaced (n=2 at baseline). From each age group in each HSC, 20 of the 31 children were randomly selected to be measured for anthropometry. At endline only, 17 children in each HSC from the older age group who received the household survey and anthropometry were chosen using SRS to be tested using direct child assessments, through game-like interactions with each child (refer to *Measurements* section). Because additional funding was obtained after the baseline was completed, direct child assessments were performed only at endline (Figure 5.1).

During the survey, supervisors conducted 10% back-checks that involved re-interviewing the caregiver on a random subset of questions and comparing results with the field investigators' results, and 10% spot-checks that involved observing interviews.

5.3.3 Intervention

The counseling and Jeevan Jyoti MNPs were delivered at no cost to households with a child 6 to 18 months of age, by the local community front-line health workers (FLWs), the Accredited Social Health Activists (ASHA) and the Anganwadi Workers (AWWs). ASHAs are local women trained as health educators under the Ministry of Health. AWWs are part of the Integrated Child Development

Services program in India; in addition to family planning and nutrition counseling and supplementation, they administer preschool activities for children 3-5 years of age. Each HSC is home to approximately seven ASHAs and seven AWWs. Typically, a pair of one AWW and one ASHA work within one Anganwadi Center (AWC) catchment area. The project area included a total of roughly 10,000 children.

FLWs were advised to provide all households (intervention and control communities) with counseling and information pamphlets on infant and young child feeding (IYCF) practices that included guidance on breastfeeding, food variety, frequency of feeding, food consistency, food quantity, hand washing and hygiene practices.

In intervention communities, FLWs distributed a box of 30 MNP sachets to the caregivers of children 6-18 months of age on a monthly basis and provided instructions to mix one MNP sachet into the child's food every day. Each MNP sachet contained 12.5mg of iron as ferrous fumarate, 5mg of zinc gluconate, 0.16mg of folic acid, 0.3mg of vitamin A acetate, 30mg of ascorbic acid, 0.9µg of vitamin B12, and 90µg of iodine (roughly one Recommended Dietary Allowance (23) for most nutrients). Children aged in and out of the program during its one-year duration depending on their age. FLWs were advised to provide 4 boxes of MNP to children during each of time periods of 6-12 and 12-18 months in accordance with World Health Organization recommendations (21). In intervention communities, the IYCF pamphlet also included detailed graphic instructions on use of MNPs. Over the project period, monthly meetings were held at the HSC-level between CARE project staff and FLWs to go over the program, the proper use of MNP sachets and their distribution, the IYCF counseling, and collection of monitoring data.

5.3.4 Masking and Training

Both data collection and data entry were masked to the intervention. Data collectors were present in the communities only before and after the intervention.

The data collection team comprised supervisors, household survey data collectors, anthropometry/hemoglobin data collectors, and research assistants for the direct child assessments. All had received minimal information on the nutrition program but were not informed about experimental group assignment. All had at least completed secondary school. Local research assistants conducting direct child assessments were bachelors, masters, or PhD students in Psychology or Social Science. All data collectors and research assistants were trained in their respective work over a two-week period. The questionnaire and direct child assessment tasks were pilot tested on children from Bihar and adapted prior to starting the survey. Training on direct child assessments was performed by L.M.L. and a local psychologist. Ongoing monitoring ensured adherence to study protocols.

5.3.5 Ethical considerations

Written informed consent (or thumb print from participants unable to write their name) was obtained from all caregivers participating in the survey. Participants were informed that the decision to participate was entirely theirs and that, if they chose to participate, they could withdraw at any time. Refusal to participate in the survey did not exclude them from receiving the MNPs or other services from the FLWs they would normally receive. Consent for child anthropometry, hemoglobin, and direct child development assessments was obtained separately, as these data were obtained in a subset of the children; caregivers could opt out of having these measurements, and still be included in the general components of the survey. A Data Safety and Monitoring Board reviewed study conduct, progress and

potential adverse effects. Child morbidity (fever, cough, rashes, or diarrhea in the past two weeks), hospitalizations, and mortality did not increase throughout the study.

5.3.6 Measurements

All questionnaires and tasks were administered in Hindi or Bhojpuri, the local dialect, based on the fluency of the respondent. The questionnaire was translated and back-translated to ensure the language was correct. Data collectors read all questions aloud to mothers or caregivers.

Developmental Milestones. Child development was assessed at baseline and endline using the DMC-II, a 75-item parent report of gross and fine motor, language, and personal-social development (24). A subset of the DMC along with seven cognitive items showed convergent validity against the Bayley Scales of Infant and Toddler Development (25). Motor development includes the sum of scores from the gross and fine motor subscales; mental development includes the sum of scores from the language, personal-social, and cognitive subscales. Items were scored as 1 if the child had performed this activity and 0 if the child had not yet performed it. This measure has been validated in India, Burkina Faso, Kenya, and Ghana (24, 26-29).

Executive Function. Direct child assessments were performed at endline only on children 12 to 18 months of age. Research assistants worked in pairs; one interacted with the child while the other took notes and scored the measure. In the A-not-B task (30), the child is shown a desirable object hidden under a cloth (location A), within the child's reach. After a brief delay, the child is allowed to search for and find the object. After several successes finding the object at a particular location, the object is then hidden under a cloth at an alternate location (B). Here, correct performance depends on the child's ability to update their memory of the hiding place as well as to inhibit the response of searching at the location where the object was previously found. Children were asked to sit on the

caregiver's lap, equidistant from the cloths. Immediately after the toy was placed under a cloth, the delay period began. Children were scored as making an error if they reached to the empty cloth, if they did not reach at all over the course of 30 seconds, or if they reached simultaneously to both cloths. Initial side of hiding (left or right) was counterbalanced across children and visits, and side of hiding was reversed after every two consecutive successes. The first reversal trial had no delay. No reversal trial was administered until the child reached correctly on the two trials prior to the reversal. Each child was given four trial attempts to retrieve the object successfully under a given delay. If the child was successful in retrieving the object on two consecutive trials, the side of hiding was changed and the delay incremented by 3 seconds. This was continued until the child failed to retrieve the object on two consecutive trials or the maximum of 12 seconds delay was successfully passed (delays: 0, 3, 6, 9, 12 seconds) (**Supplemental Figure 5.1**).

Memory Test. In the Elicited Imitation task (31, 32), which measures episodic memory, the child was tested for immediate and delayed recall of two 2-step tasks and two 3-step sequences of action. For each sequence, the child was allowed to manipulate the objects for 30 seconds. Any actions completed during this time were recorded as "baseline". Then, the research assistant, sitting in front of the child, modeled and narrated the sequence of actions in succession two times. They then returned the props to the child and invited them to imitate the exact sequence. The trial ended if the child pushed the props away or engaged in repetitive exploratory behaviors (e.g., banging the objects on the ground). The child was given two attempts to complete each sequence, if the first attempt was incomplete. Each child was tested on one 2-sequence task and one 3-sequence task immediately after modeling and one 2-sequence task and one 3-sequence task after a delay of 10 minutes (different tasks to those used for immediate recall). Ten minutes is long enough to reveal a deficit in individuals with compromised memory function due to medial-temporal lobe damage (33), and thus it is especially sensitive to the

developmental integrity of the hippocampus (31). During the delay, the examiner filled the time by conducting the immediate imitation tests. The 2-sequence tasks were 1) lift a stand and attach a foam animal to the stand, and 2) mount a slide and roll a car down the slide. The 3-sequence tasks were 1) place a ball in a cup, cover it with a top, and shake it, and 2) pivot a stand, hang a bell on the stand, and hit the bell with a mallet. To score the children's behavior, for each sequence, we calculated a total number of individual target actions produced (maximum=2 for 2-sequence tasks, maximum=3 for 3-sequence tasks) and the total number of pairs of actions produced in the target order (maximum=1 for 2-sequence tasks, maximum=2 for 3-sequence tasks). Only the first occurrence of each target action was considered so as to reduce credit that might be received due to chance or trial and error (31).

Stimulation, Diet, and Morbidity. The Family Care Indicators (FCI), a 9-item parent-report measure, previously validated in South Asia (34), was used to assess stimulating caregiving. A Wealth Index, using five categories, was calculated using Principal Component Analysis with family assets, type of household, land ownership, and source of drinking water; this was done separately for baseline and endline data. A child dietary diversity score, minimum meal frequency value, and minimum acceptable diet value were created according to WHO guidelines (35). Food deprivation was assessed through mothers' report using the cross-culturally validated Household Hunger Scale (36). Households were classified as food deprived or not based on their responses to the 4-item Likert scale. Recent morbidity was measured as any fever, cough or diarrhea in the past two weeks reported by the caregiver. Thirty-two field investigators, trained and standardized, collected the household survey information, including the DMC-II, at baseline and endline.

Anthropometry and Hemoglobin. Anthropometric measurements including weight, length, and mid-upper arm circumference (MUAC) were taken at baseline and endline following standard

procedures (37). Weight was assessed with the Seca 874 [Seca, Hamburg, Germany] and length with the Seca 417. Length-for-age, weight-for-length, and weight-for-age z-scores were calculated using the WHO 2006 child growth standards (37); z-scores less than -2 were used to define stunting, wasting, and underweight respectively; z-scores less than -3 were used to define severe stunting, severe wasting, and severe underweight. MUAC tapes (S0145620 MUAC, Child 11.5 Red/PAC-50) were used to measure MUAC. Hemoglobin was measured with the HemoCue Hb 201+ Analyzar [HemoCue, Angelholm, Sweden]. Blood samples were taken using a heel prick from children 6-11 months of age, and a finger prick for children 12-18 months. Child anemia was defined as mild if 10g/dL≤ hemoglobin <11g/dL, moderate if 7g/dL≤ hemoglobin <10g/dL, and severe if hemoglobin <7g/dL (38). If children were found to be severely anemic, they were referred to the nearest primary health center.

5.3.7 Sample size estimation

The sample size for the DMC-II outcome was based on an effect size of 0.1 or larger, 80% power, alpha of 0.05, and an intra-cluster correlation coefficient of 0.01. The required sample size was 2170 children per group, across 70 clusters. The sample size for executive function and memory was calculated to detect an effect size of 0.25 or larger, assuming a power of 0.8, an alpha of 0.05, an intra-cluster correlation coefficient of 0.2, and a refusal rate of 5%. These estimates were based on the literature on executive function and memory, and related child development interventions (39-42). The required sample size was 546 per group, across 70 clusters.

5.3.8 Statistical analyses

Data were analyzed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Children with hemoglobin measurements below 4g/dL or above or equal to 18g/dL (43) (0.2% at baseline, 0.01% at endline), or children with length-for-age z-scores <-6 or >6 (0.2% at baseline, 0.2% at endline), weight-for-length z-scores <-5 or >5 (0.6% at baseline, 0.02% at endline), or weight-for-age z-scores <-6 or >5 (0.5% at basline, 0.01% at endline) were omitted from the analysis (Figure 5.1) (44).

The effect of the intervention on change in DMC-II scores (mental and motor development, and all subscales separately) was identified by linear mixed effects models with a fixed effect of intervention group and a random effect of HSC cluster with nested AWC. We used a difference-in-difference approach to run intent-to-treat analyses (Model 1) using intervention group and age of child in months as the only fixed effects. Model 2 used fixed effects of the intervention group and age of child, covariates which were significantly different between the intervention and control communities at baseline (baseline hemoglobin and baseline household stimulation score, wealth index, maternal education, caste, and young mother status). This study used two cross-sectional surveys, and did not follow up the same children; therefore, in order to impute a baseline hemoglobin and baseline household stimulation score to endline children, we used the mean of the hemoglobin concentration and household stimulation score for children in their same cluster, stratified by gender and age group. The interaction was tested by using the standard error and denominator degrees of freedom that reflected the HSC level with nested AWC. Cohen's d effect sizes are reported for each outcome.

Effects of the intervention on executive function and memory outcomes were examined using linear and generalized linear mixed models with a fixed effect of intervention group and random effect of HSC cluster with nested AWC. Outcomes of interest on the A-not-B task were 1) ability to tolerate

3, 6, 9, and 12 seconds, or not tolerating any delay, 2) ability to find the object under cloth A, and 3) ability to find the object under cloth B. Outcomes from the Elicited Imitation tasks included 1) number of actions completed in all sequences (continuous), and 2) number of pairs of actions completed in the correct order in all sequences (continuous). All sequences were summed because there was no significant difference in the outcomes for sequences performed with or without the 10-minute delay. Performance on the tasks during the time recorded as "baseline" (pre-demonstration) was significantly different than that recorded post-demonstration indicating that the actions performed post-demonstration were due, as intended, to memory. Model 1 was intent to treat adjusting for age of the child in months, and Model 2 adjusted for the same covariates as those described for Model 2 with the DMC-II scores, in addition to child baseline mental development scores using the DMC-II as well as the research assistant testing the child. Concurrent validity of the A-not-B and Elicited Imitation tasks was examined by the associations between outcomes for each test and age of the child. Cohen's d effect sizes were calculated by taking a difference of the change in scores between groups (or difference in scores between groups for measurements only conducted at endline) divided by a pooled standard deviation.

Using Model 2, we examined effect modification on mental and motor development scores using the DMC-II and the outcomes of the A-not-B and Elicited Imitation tasks, from level of baseline household FCI stimulation (dichotomized as low v. high based on a score below/equal to or above the median score of 5) and continuous baseline hemoglobin concentrations. We also examined dose-response within the intervention group using number of MNP sachets consumed by the child in the past month (dichotomized as <10 v. ≥ 10 sachets in children from intervention communities at endline only). Baseline household FCI stimulation scores and baseline hemoglobin concentrations were imputed for endline children by taking a mean of the FCI score or hemoglobin concentration within baseline children from the same HSC of the same gender and age group. There was little (7%) overlap between

children with high baseline stimulation scores and children having consumed ≥10 MNP sachets over the past month, indicating that the two measures are examining different outcomes. Statistical significance was defined as p-value < 0.05.

5.3.9 Quality control

Reliability of the data collectors' scores was established by examining the relation between the field investigators' scores and those of an expert when assessing the same child, using five children, both at baseline and endline (37). Reliability measurements for weight, height, and MUAC yielded a Pearson's correlation coefficient between measurements of the investigators and expert of >0.92 and a coefficient of reliability (which measures the proportion of inter-subject variance due to measurement error) of >0.80. Reliability of the research assistants on direct child assessments was difficult to establish given the tasks tested executive function and memory; any re-test would have yielded biased responses from the child. Therefore, all research assistants practiced the tasks on children for three days while being observed by the trainers. Only those who performed the assessments correctly were retained.

Intra-cluster correlation coefficients for each outcome were calculated using the between and within cluster variability: <0.01 for motor, 0.02 for mental, <0.01 for gross motor, 0.03 for fine motor, 0.02 for language, 0.03 for personal-social, 0.05 for cognitive scores; 0.10 for memory scores; 0.07 for executive function scores.

5.4 Results

At baseline, 60% of mothers had no schooling, mean parity was 2.7 children, 72% of children were anemic, 33% stunted, 27% wasted, and 42% underweight. At baseline, the mean motor and mental development score among all children was 17.8 out of 32 (95% CI: 17.6, 18.0) and 24.9 out of 50 (95% CI: 24.4, 25.3), respectively. For the most part, the intervention and control groups matched on key demographic and child nutritional characteristics at baseline (**Table 5.1**). However, the intervention group had significantly higher prevalence of any maternal education, higher mean FCI score, lower mean hemoglobin concentration, and higher mean score on the cognitive subscale of the DMC-II. Among children living in intervention communities at endline, 40% received 10 or more MNP sachets over the month prior to the survey.

Validity of the DMC-II in this context is reported elsewhere (26). In a bivariate regression, outcomes on the A-not-B and Elicited Imitation tasks are significantly ($p<0.001$) associated with child age. Each month of age between 12 to 18 months was associated with a 13% (OR: 1.13, 95% CI: 1.06, 1.20) higher odds of tolerating 3 more seconds of delay before finding a hidden object in the A-not-B task, a 0.28 (95% CI: 0.22, 0.34) increase in the number of actions complete in the correct order across all Elicited Imitation sequences, and a 0.19 (95% CI: 0.15, 0,24) increase in the number of pairs of actions complete in the correct order. For the Elicited Imitation tasks, children's baseline performance (scores for actions completed prior to research assistant demonstrating the sequences) was significantly different from their post-demonstration performance for each sequence, meaning that performance was due to memory and not innate actions. These patterns are consistent with those in the wider literature using Elicited Imitation tasks (31).

DMC-II scores for mental and motor development, and for each subscale, as well as Elicited Imitation task outcomes were normally distributed. The difference-in-difference analyses for DMC-II

scores indicated that scores of children from intervention communities increased significantly more than those of control communities in gross motor, language, and personal-social development subscales ($p<0.01$) (**Table 5.2**). As a whole, the change in motor and mental development of children between the two time points was larger for intervention group children than control group children (**Supplemental Figures 5.2 & 5.3**). Examination by age showed that the change in scores for gross motor development was significantly larger in the intervention than in the control group for children 6-11 months of age, whereas the change in language development scores was significantly larger for children 12-18 months of age. Significant effect modification was seen by level of baseline household stimulation, but not by baseline hemoglobin. The effect of the intervention on motor and mental development, and language, and personal-social subscales, in children from households with high levels of stimulation was significantly more than that of children with low levels of household stimulation (**Table 5.3**). A significant dose response was observed using numbers of MNP sachets consumed by the child over the previous month. At endline, among children from the intervention communities, scores for motor and mental development, and each subscale (gross and fine motor, language, personal-social, and cognitive development) were significantly higher in children who had received 10 or more MNP sachets over the previous month compared to children who had received fewer sachets (**Table 5.4**).

In children 12-18 months of age, there was no significant impact of the intervention on the odds of tolerating a 3, 6, 9, and 12 second delay compared to no delay on the A-not-B task (**Table 5.5**). We grouped all children who tolerated any delay because a small proportion (22%) of children had a maximum tolerated delay between 0 and 12 seconds (i.e. maximum tolerated delay of 3, 6, or 9, seconds). The majority of children who were able to tolerate any delay were able to tolerate a 12 second delay. There were no significant effects of the intervention on the odds of finding the toy under cloth A or the odds of perseverative error (not finding the toy under cloth B) (Table 5.5). Similarly,

there was no effect of the intervention on memory scores (**Table 5.6**). There was no significant effect modification of the intervention from level of baseline household stimulation, baseline hemoglobin, nor was there a dose response.

5.5 Discussion

This study was an effectiveness trial of home fortification with MNPs, distributed through the existing health infrastructure in rural Bihar. Our findings indicate that the intervention had an impact on gross motor, language, and personal-social development of children 6 to 18 months of age as measured by the DMC-II. The impact on motor development was significant in younger children 6-11 months of age, and the impact on language development significant in older children 12-18 months of age. Effects were modified by the baseline household stimulation, whereby the intervention had a larger impact in children with higher compared to lower stimulation at the start of the intervention. We observed no significant effect of the intervention on executive function or memory of children 12 to 18 months of age.

The motor and language development effect sizes we observed in our study are smaller than those from a previous effectiveness trial in children 6 to 24 months of age in Pakistan in which MNPs were delivered by Lady Health Workers (7). However, in the Pakistan study, mothers of children under two years were given MNPs and nutrition education over a period of 18 months, which is longer than the current study. Another effectiveness trial in Bangladesh utilized staff from a community health and development program provided iron and folic acid supplements during monthly home visits to mothers during pregnancy and 3 months postpartum and a 15-nutrient MNP to the child from 6 to 24 months of age (9). The trial found a significant impact on motor and language development, but no impact on personal-social development (9).

In younger children 6 to 11 months of age, significant improvements were observed in the gross motor subscale from baseline to endline in the intervention group compared to the control group; whereas in children 12 to 18 months, significant improvements were observed in the language development subscale. These findings suggest that infants' gross motor abilities were sensitive to the MNP supplementation from an early age, which may be because motor skills change more rapidly in the first year rather than the second year of life (45-47). Even though younger children would have received MNPs for a shorter time period than older children, there is potential to benefit gross motor skills. Gross motor development itself has value for a young child in terms of increasing mobility; enhanced mobility can increase mental development especially if it raises the amount of environmental stimulation accessed by the child. The benefit to language development seen only in children after 12 months may be due to MNPs contributing to the 'language explosion' seen in the second and third year of life (48) or to mothers' greater awareness of their child's language development due to enhancement of children's overt speech at this age. Previous research has shown a similar impact of nutrition on expressive language in children above one year of age. A recent cluster randomized trial in Bangladesh which provided MNPs to children between 7 and 12 months of age and followed them up at 16-22 months of age found improvements in expressive, but not receptive, language development (10). Standard deviations of scores are similar across both age groups in our sample, showing that children are not reaching a ceiling or floor score at the tail ends of the age range. The score was able to capture variability from 6 to 18 months of age. It is worth noting that many children in this population begin complementary feeding later than recommended (26); only children who had begun complementary feeding would have been exposed to the MNPs, which were designed to be mixed into the child's food.

Similarly to other recent nutrition interventions (9, 49-51), we did not find significant effects of the intervention on executive function or memory. The measures of executive function and memory could be insensitive to an MNP intervention in this age group (12 to 18 months of age), but effects may

become apparent later throughout childhood. In infancy, executive functions are undifferentiated, or unrefined (52). Over the course of development, as a function of experience-dependent neural-specialization, executive function differentiates into constructs, namely working memory, cognitive flexibility, and inhibitory control (52, 53). In addition, executive function differentiates from other cognitive functions, such as episodic memory (54). Therefore, as cognitive functions differentiate, the effects of a nutrition intervention may become apparent on unique constructs. Executive function and memory are important predictors of school readiness and academic achievement (54-56), even more so than IQ. As such, greater understanding of their response to nutrition interventions in early life should be prioritized for further research.

Our findings indicate that the intervention had a stronger impact on motor and mental development of children with a higher level of stimulation at baseline, suggesting that a minimum level of stimulation and resources at home are required before MNP interventions can provide benefits to development. These findings are consistent with the synergistic effect of stimulation and nutrition in early childhood. For instance, an effectiveness trial of iodized salt in Ethiopia found benefits of the intervention on mental development of children if their mothers had attended school (57). Another study in Mexico resulted in larger impact of a group-based parenting program on language development in children of mothers with any formal education compared to no education (58). This threshold hypothesis is also supported by the literature showing larger gains in language and literacy outcomes from increases in quality of instruction for children from higher quality classrooms compared to those from lower quality classrooms (59).

Strengths of the study included its large sample size and cluster randomized design which allowed comparison across intervention and control communities. Clustering resulted in little contamination across groups. The use and validation of the tools to assess infant and young child development in rural northern India is an important addition to the literature. The DMC-II can be

administered by trained non-specialists, and is a simple and quick measure of global development. The A-not-B and Elicited Imitation tasks require specialized training, but performed well in this context. Limitations of the study include the two cross-sectional surveys from baseline to endline rather than a follow-up of the same children. A longitudinal sample would have revealed differences in development outcomes on the same children and reduced confounding by having every child serve as their own control. The timing of funding for the additional executive function and memory outcomes prevented us from measuring these cognitive functions at baseline. The lack of baseline measures precluded a difference-in-difference analysis. Mothers were not masked to the intervention, and responses to the parent report DMC-II could have been biased by their expectations of the MNPs. However, data collectors were masked and would not have provoked a biased response.

The study's significant impact on child development is important to inform the IFHI and other state level nutrition and early child development initiatives. The impact we observed on motor and mental development from the intervention is equivalent to 10 and 16 days of development, respectively, when we compare the observed estimates of the effects to the change in development scores by child age in months. Despite the moderate coverage of the intervention, these achievements are important in the context of a state with extremely poor nutritional indicators and extreme poverty. Further, the threshold effect we see from stimulation indicates that programs addressing both stimulation and nutrition could have important implications on early child development.

5.6 Acknowledgements

We have no conflicts of interest relevant to this article to disclose. Funding support provided by a Bill and Melinda Gates Foundation grant through a subcontract with CARE India and the Thrasher Research Fund. We wish to thank Priya Kekre for her contribution to the coordination of the study and

data collection. Also, we wish to thank our collaborators, CARE India, as well as the women and children who participated in this study. Finally, we thank the Laney Graduate School at Emory University for funding LML while she pursues her PhD. The authors' responsibilities were as follows: LML designed the child development component of the study, supervised data collection, analyzed the data, and drafted the initial manuscript; RM coordinated the study in the field; MFY, PJB, UR, AWG, PV, IC, SS, and RM contributed to the design of the study, supervised data collection, and critically reviewed the manuscript. SS and RM secured funding from the Bill and Melinda Gates Foundation, and RM, LML, and MFY secured funding from the Thrasher Research Fund for the study. All authors read and approved the final manuscript as submitted. None of the authors declare a conflict of interest with regard to this manuscript.

5.7 Chapter 5 references

1. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, Lu C, McCoy DC, Fink G, Shawar YR, Shiffman J, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389(10064):77-90. doi: 10.1016/s0140-6736(16)31389-7.
2. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369(9555):60-70. doi: 10.1016/s0140-6736(07)60032-4.
3. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet 2013;382(9890):427-51.
4. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72(4):267-84. doi: 10.1111/nure.12102.
5. Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol 2015;66:433-57. doi: 10.1146/annurev-psych-010814-015128.
6. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children under-two in low- and middle-income countries. Maternal & child nutrition 2017;13(1). doi: 10.1111/mcn.12229.
7. Yousafzai AK, Aboud F. Review of implementation processes for integrated nutrition and psychosocial stimulation interventions. Annals of the New York Academy of Sciences 2014;1308:33-45. doi: 10.1111/nyas.12313.
8. Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. The Lancet 2014.
9. Matias SL, Mridha MK, Tofail F, Arnold CD, Khan MS, Siddiqui Z, Ullah MB, Dewey KG. Home fortification during the first 1000 d improves child development in Bangladesh: a cluster-randomized effectiveness trial. The American journal of clinical nutrition 2017. doi: 10.3945/ajcn.116.150318.
10. Singla DR, Shafique S, Zlotkin SH, Aboud FE. 25-element micronutrient powder benefits language but not cognition in Bangladeshi full term low birth weight children1. Journal of Nutrition 2014.
11. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. The American journal of clinical nutrition 2007;85(2):614s-20s.
12. Colombo J. Infant cognition: Predicting later intellectual functioning: Sage publications, 1993.
13. Kail R. Developmental functions for speeds of cognitive processes. Journal of Experimental Child Psychology 1988;45(3):339-64.
14. Wainwright PE, Colombo J. Nutrition and the development of cognitive functions: interpretation of behavioral studies in animals and human infants. The American journal of clinical nutrition 2006;84(5):961-70.
15. Christian P, Murray-Kolb LE, Tielsch JM, Katz J, LeClerq SC, Khatry SK. Associations between preterm birth, small-for-gestational age, and neonatal morbidity and cognitive function among school-age children in Nepal. BMC pediatrics 2014;14:58. doi: 10.1186/1471-2431-14-58.
16. Diamond A, Prevor MB, Callender G, Druin DP. Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. Monographs of the Society for Research in Child Development 1997;62(4):i-v, 1-208.

17. Burden MJ, Westerlund AJ, Armony-Sivan R, Nelson CA, Jacobson SW, Lozoff B, Angelilli ML, Jacobson JL. An event-related potential study of attention and recognition memory in infants with iron-deficiency anemia. Pediatrics 2007;120(2):e336-e45.
18. Colombo J, Zavaleta N, Kannass KN, Lazarte F, Albornoz C, Kapa LL, Caulfield LE. Zinc Supplementation Sustained Normative Neurodevelopment in a Randomized, Controlled Trial of Peruvian Infants Aged 6–18 Months. The Journal of nutrition 2014:jn. 113.189365.
19. Nelson CA, Wewerka S, Thomas KM, deRegnier R-a, Tribbey-Walbridge S, Georgieff M. Neurocognitive sequelae of infants of diabetic mothers. Behavioral neuroscience 2000;114(5):950.
20. International Institute of Population Sciences. National Family Health Survey (NFHS-4), 2015-2016: India. 2016.
21. WHO. Guideline: use of multiple micronutrient powders for home fortification of foods consumed by infants and children 6-23 months of age. Geneva. http://whqlibdoc.who.int/publications/2011/9789241502047_eng.pdf.: World Health Organization, 2011.
22. Young M, Kekre P, Verma P, Sheth M, Kumar A, Trehan S, Chaudhuri I, Majumdar A, Webb-Girard A, Ramakrishnan U, et al. A formative research study for home fortification of complementary foods under Integrated Family Health Program: Process and methodology. Micronutrient Forum. Addis Ababa, Ethiopia, 2014.
23. NIN. Nutrient requirements and recommended dietary allowances for Indians. A report of the Expert Group of the Indian Council of Medical Research. Hyderabad, India, 2010.
24. Prado EL, Abubakar AA, Abbeddou S, Jimenez EY, Some JW, Ouedraogo JB. Extending the Developmental Milestones Checklist for use in a different context in Sub-Saharan Africa. Acta paediatrica (Oslo, Norway : 1992) 2014;103(4):447-54. doi: 10.1111/apa.12540.
25. Bayley N. Bayley Scales of Infant Development Manual. Third ed. Antonio, TX: The Psychological Corporation, 2006.
26. Larson LM, Young MF, Ramakrishnan U, Webb Girard A, Verma P, Chaudhuri I, Srikantiah S, Martorell R. A Cross-Sectional Survey in Rural Bihar, India, Indicates That Nutritional Status, Diet, and Stimulation Are Associated with Motor and Mental Development in Young Children. The Journal of nutrition 2017;147(8):1578-85. doi: 10.3945/jn.117.251231.
27. Prado EL, Abbeddou S, Yakes Jimenez E, Some JW, Ouedraogo ZP, Vosti SA, Dewey KG, Brown KH, Hess SY, Ouedraogo JB. Lipid-Based Nutrient Supplements Plus Malaria and Diarrhea Treatment Increase Infant Development Scores in a Cluster-Randomized Trial in Burkina Faso. The Journal of nutrition 2016. doi: 10.3945/jn.115.225524.
28. Abubakar A, Holding P, Van de Vijver F, Bomu G, Van Baar A. Developmental monitoring using caregiver reports in a resource-limited setting: the case of Kilifi, Kenya. Acta paediatrica (Oslo, Norway : 1992) 2010;99(2):291-7. doi: 10.1111/j.1651-2227.2009.01561.x.
29. Ahun M. Maternal and child health and development in rural Ghana. Department of Psychology. Montreal, Quebec: McGill University, 2015.
30. Diamond A. Development of the ability to use recall to guide action, as indicated by infants' performance on AB. Child development 1985;56(4):868-83.
31. Bauer PJ. Declarative memory in infancy: an introduction to typical and atypical development. Advances in child development and behavior 2010;38:1-25.
32. Bauer PJ. New developments in the study of infant memory. Handbook of research methods in developmental science 2005:467-88.
33. Reed JM, Squire LR. Retrograde amnesia for facts and events: findings from four new cases. Journal of Neuroscience 1998;18(10):3943-54.

34. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. Journal of health, population, and nutrition 2010;28(1):23.
35. WHO. Indicators for assessing infant and young child feeding practices: part 1: definitions. Geneva. http://apps.who.int/iris/bitstream/10665/43895/1/9789241596664_eng.pdf: World Health Organization, 2008.
36. Ballard T, Coates J, Swindale A, Deitchler M. Household hunger scale: indicator definition and measurement guide. Food and Nutrition Technical Assistance II Project, FHI 2011;360.
37. de Onis M, Onyango AW, Van den Broeck J, Chumlea WC, Martorell R. Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference. Food and nutrition bulletin 2004;25(1 Suppl):S27-36.
38. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva. http://www.who.int/vmnis/indicators/haemoglobin.pdf: World Health Organization, 2011.
39. Sun J, Mohay H, O'Callaghan M. A comparison of executive function in very preterm and term infants at 8 months corrected age. Early human development 2009;85(4):225-30. doi: 10.1016/j.earlhumdev.2008.10.005.
40. Heathcock JC, Bhat AN, Lobo MA, Galloway JC. The performance of infants born preterm and full-term in the mobile paradigm: learning and memory. Phys Ther 2004;84(9):808-21.
41. Portillo-Reyes V, Perez-Garcia M, Loya-Mendez Y, Puente AE. Clinical significance of neuropsychological improvement after supplementation with omega-3 in 8-12 years old malnourished Mexican children: a randomized, double-blind, placebo and treatment clinical trial. Res Dev Disabil 2014;35(4):861-70. doi: 10.1016/j.ridd.2014.01.013.
42. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 2013;382(9890):452-77. doi: 10.1016/s0140-6736(13)60996-4.
43. Sullivan KM, Mei Z, Grummer-Strawn L, Parvanta I. Haemoglobin adjustments to define anaemia. Trop Med Int Health 2008;13(10):1267-71. doi: 10.1111/j.1365-3156.2008.02143.x.
44. WHO. WHO Child Growth Standards SAS igrowup package. Geneva. http://www.who.int/childgrowth/software/readme_sas.pdf: World Health Organization, 2011.
45. Thelen E. Developmental origins of motor coordination: leg movements in human infants. Developmental psychobiology 1985;18(1):1-22. doi: 10.1002/dev.420180102.
46. Wijnhoven TM, de Onis M, Onyango AW, Wang T, Bjoerneboe GE, Bhandari N, Lartey A, al Rashidi B. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food and nutrition bulletin 2004;25(1 Suppl):S37-45. doi: 10.1177/15648265040251s105.
47. Rubio-Codina M, Araujo MC, Attanasio O, Munoz P, Grantham-McGregor S. Concurrent Validity and Feasibility of Short Tests Currently Used to Measure Early Childhood Development in Large Scale Studies. PLoS One 2016;11(8):e0160962. doi: 10.1371/journal.pone.0160962.
48. McMurray B. Defusing the childhood vocabulary explosion. Science (New York, NY) 2007;317(5838):631. doi: 10.1126/science.1144073.
49. Prado EL, Maleta K, Ashorn P, Ashorn U, Vosti SA, Sadalaki J, Dewey KG. Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi. The American journal of clinical nutrition 2016;103(3):784-93. doi: 10.3945/ajcn.115.114579.

50. Warthon-Medina M, Qualter P, Zavaleta N, Dillon S, Lazarte F, Lowe NM. The Long Term Impact of Micronutrient Supplementation during Infancy on Cognition and Executive Function Performance in Pre-School Children. Nutrients 2015;7(8):6606-27. doi: 10.3390/nu7085302.
51. Yousafzai AK, Obradovic J, Rasheed MA, Rizvi A, Portilla XA, Tirado-Strayer N, Siyal S, Memon U. 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. The Lancet Global health 2016;4(8):e548-58. doi: 10.1016/s2214-109x(16)30100-0.
52. Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Weintraub S. II. NIH Toolbox Cognition Battery (CB): measuring executive function and attention. Monographs of the Society for Research in Child Development 2013;78(4):16-33. doi: 10.1111/mono.12032.
53. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cognitive psychology 2000;41(1):49-100. doi: 10.1006/cogp.1999.0734.
54. Bauer PJ, Dikmen SS, Heaton RK, Mungas D, Slotkin J, Beaumont JL. III. NIH Toolbox Cognition Battery (CB): measuring episodic memory. Monographs of the Society for Research in Child Development 2013;78(4):34-48. doi: 10.1111/mono.12033.
55. Blair C, Razza RP. Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. Child development 2007;78(2):647-63. doi: 10.1111/j.1467-8624.2007.01019.x.
56. Eigsti IM, Zayas V, Mischel W, Shoda Y, Ayduk O, Dadlani MB, Davidson MC, Lawrence Aber J, Casey BJ. Predicting cognitive control from preschool to late adolescence and young adulthood. Psychological science 2006;17(6):478-84. doi: 10.1111/j.1467-9280.2006.01732.x.
57. Aboud FE, Bougma K, Lemma T, Marquis GS. Evaluation of the effects of iodized salt on the mental development of preschool-aged children: a cluster randomized trial in northern Ethiopia. Maternal & child nutrition 2016. doi: 10.1111/mcn.12322.
58. Fernald LC, Kagawa RM, Knauer HA, Schnaas L, Guerra AG, Neufeld LM. Promoting child development through group-based parent support within a cash transfer program: Experimental effects on children's outcomes. Dev Psychol 2017;53(2):222-36. doi: 10.1037/dev0000185.
59. Zaslow M, Anderson R, Redd Z, Wessel J, Daneri P, Green K, Cavadel EW, Tarullo L, Burchinal M, Martinez-Beck I. I. Quality thresholds, features, and dosage in early care and education: introduction and literature review. Monographs of the Society for Research in Child Development 2016;81(2):7-26. doi: 10.1111/mono.12236.

Table 5.1: Demographic and clinical characteristics of children at baseline and endline by intervention group

		Baseline		Endline	
		Intervention group (N=2184)	**Control group (N=2176)**	**Intervention group (N=2170)**	**Control group (N=2122)**
Household characteristics	Religion				
	Hindu	78.1 (1701)	79.5 (1730)	75.7 (1646)	78.0 (1655)
	Muslim	21.9 (478)	20.5 (445)	24.3 (529)	22.0 (466)
	Mean (SD) maternal age (years)	25.2 ± 4.7	25.2 ± 4.8	25.0 ± 4.7	25.2 ± 4.7
	Mean (SD) paternal age (years)	29.5 ± 5.7	29.4 ± 5.9	28.9 ± 5.3	29.3 ± 5.5
	Maternal education				
	Any schooling	42.1 (918)	37.7 (819)	48.0 (1043)	44.9 (952)
	Paternal education				
	Any schooling	65.1 (1417)	62.8 (1360)	68.2 (1453)	67.4 (1397)
	Caste				
	Scheduled Caste	24.1 (524)	26.4 (572)	18.1 (394)	21.0 (446)
	Scheduled Tribe	7.3 (159)	9.3 (201)	7.2 (156)	11.3 (241)
	Other Backwards Caste	17.0 (370)	15.0 (325)	13.7 (298)	11.0 (234)
	Mean (SD) parity	2.7 ± 1.6	2.7 ± 1.6	2.6 ± 1.6	2.7 ± 1.6
	Mean (SD) Family Care Indicators score (out of 13)	5.2 ± 2.3	5.0 ± 2.3	5.3 ± 1.7	5.2 ± 1.5
Child characteristics	Age				
	6-11 months	50.2 (1096)	51.1 (1111)	46.9 (1021)	46.3 (983)
	12-18 months	49.8 (1087)	48.9 (1065)	53.1 (1154)	53.7 (1141)
	Mean (SD) age in months	11.3 ± 3.2	11.2 ± 3.1	11.7 ± 3.5	11.7 ± 3.5
	Gender				
	Girls	48.7 (1062)	50.8 (1103)	47.2 (1026)	46.6 (990)
	Mean (SD) dietary diversity score (out of 7)	2.7 ± 1.1	2.8 ± 1.1	3.6 ± 1.6	3.6 ± 1.6
	Minimum meal frequency achieved	64.5 (1380)	67.1 (1428)	71.8 (1418)	75.1 (1451)
	Minimum acceptable diet achieved	14.4 (314)	16.0 (348)	22.3 (486)	23.1 (491)
	Any household hunger	9.7 (209)	9.3 (201)	4.3 (93)	4.6 (97)
	Any recent child morbidity	75.2 (1642)	76.2 (1658)	51.7 (1125)	54.4 (1157)
	Fever	64.8 (1415)	67.0 (1459)	34.7 (755)	37.6 (799)
	Cough	54.3 (1184)	55.5 (1205)	39.5 (859)	39.4 (837)
	Diarrhea	11.6 (253)	12.1 (263)	11.1 (241)	15.6 (331)
	Anthropometry				
	Mean (SD) length-for-age z-score	-1.49 ± 1.3	-1.49 ± 1.3	-1.36 ± 1.2	-1.38 ± 1.2
	Mean (SD) weight-for-length z-score	-1.34 ± 1.1	-1.35 ± 1.2	-0.83 ± 1.0	-0.91 ± 1.0
	Mean (SD) weight-for-age z-score	-1.80 ± 1.1	-1.82 ± 1.1	-1.32 ± 1.1	-1.40 ± 1.1

	Mean (SD) mid-upper-arm-circumference	13.14 ± 1.1	13.13 ± 1.1	13.62 ± 1.0	13.57 ± 1.0
Anemia					
	Any (hemoglobin < 11g/dL)	75.3 (1062)	69.2 (977)	64.4 (910)	66.1 (934)
	Mild (10 g/dL ≤ hemoglobin < 11 g/dL)	27.5 (388)	28.4 (401)	30.8 (435)	32.0 (453)
	Moderate (7 g/dL ≤ hemoglobin < 10 g/dL)	44.8 (632)	38.5 (543)	32.4 (458)	33.5 (473)
	Severe (hemoglobin < 7 g/dL)	3.0 (42)	2.3 (33)	1.2 (17)	0.6 (8)
	Mean (SD) Hemoglobin (g/dL)	9.9 ± 1.5	10.2 ± 1.6	10.4 ± 1.4	10.4 ± 1.4

[1]Values are % (N) or mean ± SD. At baseline, total N=4360 for all measurements except for anthropometry and anemia, for which N=2838. At endline, total N=4292 for all measurements except for anthropometry and anemia, for which N=2826. Minimum meal frequency is achieved if a breastfed child is fed at least three times or a non-breastfed child is fed at least four times the previous day. Minimum acceptable diet is achieved if a breastfed child is fed four or more food groups and achieved minimum meal frequency or a non-breastfed child received at least two milk feeds, is fed four or more foods groups and achieved minimum meal frequency the previous day. CI, confidence interval; SD, standard deviation; WASH, Water, sanitation, and hygiene.

Table 5.2: Mean DMC-II scores for children 6-18 months of age at baseline and endline by intervention group[1]

	Baseline[2]		Endline[2]					
	Intervention (N=2184)	Control (N=2176)	Intervention (N=2170)	Control (N=2122)	Model 1		Model 2	
					Effect size[3]	P-value	Effect size[3]	P-value
All children								
Motor development (out of 32)	17.8 ± 5.4	17.9 ± 5.3	18.8 ± 6.6	18.5 ± 6.4	0.13 (0.05, 0.21)	0.003	0.12 (0.03, 0.22)	0.01
Mental development (out of 50)	24.9 ± 6.8	24.8 ± 6.8	26.2 ± 7.5	25.4 ± 7.5	0.16 (0.07, 0.24)	<0.001	0.15 (0.06, 0.25)	0.002
Gross motor (out of 22)	11.1 ± 4.0	11.1 ± 4.0	12.1 ± 4.9	11.9 ± 4.7	0.15 (0.07, 0.23)	0.001	0.15 (0.06, 0.25)	0.002
Fine motor (out of 10)	6.7 ± 1.9	6.7 ± 1.9	6.6 ± 2.1	6.6 ± 2.0	0.04 (-0.04, 0.13)	0.31	0.02, -0.08, 0.12)	0.69
Language (out of 15)	4.6 ± 2.5	4.6 ± 2.5	5.4 ± 2.7	5.1 ± 2.6	0.16 (0.07, 0.24)	<0.001	0.17 (0.07, 0.26)	0.001
Personal-social (out of 28)	16.1 ± 3.7	16.2 ± 3.7	16.5 ± 4.1	16.2 ± 4.0	0.14 (0.06, 0.23)	0.001	0.13 (0.04, 0.23)	0.01
Cognitive (out of 7)	4.2 ± 1.6	4.1 ± 1.6	4.3 ± 1.7	4.1 ± 1.7	0.07 (-0.02, 0.15)	0.13	0.05 (-0.04, 0.15)	0.29
Children 6-11 months of age								
Motor development (out of 32)	14.5 ± 4.0	15.0 ± 4.2	13.7 ± 4.7	13.6 ± 4.6	0.14 (0.02, 0.26)	0.02	0.16 (0.02, 0.29)	0.02
Mental development (out of 50)	21.6 ± 5.8	21.7 ± 5.9	21.1 ± 6.5	20.3 ± 6.3	0.14 (0.02, 0.26)	0.02	0.14 (0.01, 0.28)	0.04
Gross motor (out of 22)	8.6 ± 2.6	9.0 ± 2.9	8.3 ± 3.2	8.2 ± 3.1	0.16 (0.04, 0.28)	0.01	0.19 (0.05, 0.32)	0.01
Fine motor (out of 10)	5.9 ± 1.9	6.0 ± 1.9	5.4 ± 2.0	5.3 ± 1.9	0.07 (-0.05, 0.19)	0.27	0.06 (-0.07, 0.20)	0.37
Language (out of 15)	3.4 ± 2.0	3.5 ± 1.9	3.6 ± 2.0	3.4 ± 1.9	0.08 (-0.04, 0.21)	0.17	0.09 (-0.05, 0.23)	0.19
Personal-social (out of 28)	14.5 ± 3.4	14.7 ± 3.5	13.9 ± 3.7	13.6 ± 3.6	0.14 (0.02, 0.26)	0.03	0.13 (-0.01, 0.27)	0.07
Cognitive (out of 7)	3.7 ± 1.6	3.6 ± 1.6	3.6 ± 1.8	3.3 ± 1.8	0.11 (-0.01, 0.23)	0.07	0.11 (-0.02, 0.25)	0.11
Children 12-18 months of age								
Motor development (out of 32)	21.1 ± 4.5	20.9 ± 4.5	23.2 ± 4.4	22.7 ± 4.4	0.10 (-0.02, 0.22)	0.09	0.08 (-0.06, 0.21)	0.26
Mental development (out of 50)	28.3 ± 6.0	28.1 ± 6.1	30.7 ± 5.1	29.8 ± 5.3	0.16 (0.04, 0.28)	0.01	0.16 (0.02, 0.29)	0.02
Gross motor (out of 22)	13.6 ± 3.6	13.4 ± 3.7	15.5 ± 3.5	15.0 ± 3.5	0.13 (0.02, 0.25)	0.03	0.12 (-0.02, 0.25)	0.09
Fine motor (out of 10)	7.5 ± 1.5	7.5 ± 1.5	7.7 ± 1.5	7.7 ± 1.4	-0.01 (-0.13, 0.11)	0.88	-0.05 (-0.18, 0.09)	0.49
Language (out of 15)	5.8 ± 2.4	5.8 ± 2.5	6.9 ± 2.1	6.5 ± 2.2	0.21 (0.09, 0.33)	0.001	0.22 (0.08, 0.35)	0.002

Personal-social (out of 28)	17.8 ± 3.3	17.7 ± 3.3	18.8 ± 2.8	18.4 ± 2.9	0.13 (0.01, 0.25)	0.03	0.13 (0.00, 0.26)	0.06
Cognitive (out of 7)	4.7 ± 1.4	4.5 ± 1.5	5.0 ± 1.3	4.8 ± 1.3	0.00 (-0.12, 0.12)	0.97	-0.02 (-0.15, 0.11)	0.78

[1]All models account for clustering by Health Sub-Center and nested Anganwadi Center. Model 1 is adjusting for age of child. Model 2 is adjusting for age of child, baseline hemoglobin, baseline home stimulation score, wealth index, maternal education, caste, and young mother. Effect sizes are calculated with adjusted means. Children 6-11 months N=2208 at baseline and N=2004 at endline; children 12-18 months of age N=2152 at baseline and N=2288 at endline. CI, confidence interval; SD, standard deviation.
[2]Values are raw mean±SD
[3]Values are effect size (95% CI)

Table 5.3: Effect size for change in DMC-II scores from baseline to endline by intervention group for children from low compared to high stimulation households[1]

	Low stimulation at baseline[2]	**High stimulation at baseline[2]**	**P-value**
Motor development (out of 32)	0.09 (-0.04, 0.22)	0.20 (0.05, 0.34)	0.004
Mental development (out of 50)	0.14 (0.01, 0.27)	0.22 (0.08, 0.37)	<0.001
Gross motor (out of 22)	0.14 (0.01, 0.26)	0.21 (0.06, 0.35)	0.11
Fine motor (out of 10)	-0.04 (-0.17, 0.10)	0.13 (-0.01, 0.27)	<0.001
Language (out of 15)	0.15 (0.03, 0.28)	0.22 (0.07, 0.36)	<0.001
Personal-social (out of 28)	0.11 (-0.02, 0.25)	0.20 (0.06, 0.34)	<0.001
Cognitive (out of 7)	0.06 (-0.08, 0.19)	0.10 (-0.04, 0.24)	<0.001

[1]Accounting for clustering by Health Sub-Center and nested Anganwadi Center. Analysis is adjusted for age of child, baseline hemoglobin, baseline home stimulation score, wealth index, maternal education, caste, and young mother. Scores were divided by low and high stimulation based on below or above median baseline value (≤5 vs >5). Low home stimulation N=2025; high home stimulation N=2273.
[2]Values are effect size (95% CI)

Table 5.4: Mean DMC-II scores for children 6-18 months of age in intervention group at endline by consumption of Jeevan Jyoti in the past one month[1]

	<10 sachets/month	**>= 10 sachets/month**
Motor development (out of 32)	18.4 ± 6.7	20.0 ± 5.8
Mental development (out of 50)	25.6 ± 7.8	28.1 ± 6.3
Gross motor (out of 22)	11.9 ± 5.0	13.0 ± 4.5
Fine motor (out of 10)	6.5 ± 2.1	7.1 ± 1.8
Language (out of 15)	5.2 ± 2.7	5.9 ± 2.4
Personal-social (out of 28)	16.2 ± 4.2	17.5 ± 3.5
Cognitive (out of 7)	4.2 ± 1.8	4.7 ± 1.4

[1]Values are raw mean±SD. P-value <0.001 for all. Accounting for clustering by Health Sub-Center and nested Anganwadi Center. Analysis is adjusting for age of child, baseline hemoglobin, baseline home stimulation score, wealth index, maternal education, caste, and young mother. Analysis includes only children at endline from the intervention group. Fewer than 10 sachets/month N=1643; more than or equal to 10 sachets/month N=531. SD, standard deviation.

Table 5.5: Odds ratios of executive function outcomes among children 12 to 18 months of age from intervention compared to control group (N=1079)[1]

	Intervention[2]	Control[2]	Model 1[3]	P-value	Model 2[3]	P-value
Tolerated delay						
None	42.8 (248)	37.3 (215)	ref		ref	
Any	57.2 (332)	62.7 (362)	0.82 (0.62, 1.1)	0.27	0.79 (0.59, 1.05)	0.10
Not found under cloth A	26.1 (153)	22.9 (134)	ref		ref	
Found under cloth A	73.9 (434)	77.1 (451)	0.85 (0.57, 1.25)	0.33	0.80 (0.55, 1.15)	0.22
Perseverative error	32.2 (189)	28.2 (165)	ref		ref	
Found under cloth B	67.8 (398)	71.8 (420)	0.83 (0.60, 1.16)	0.23	0.82 (0.59, 1.14)	0.23

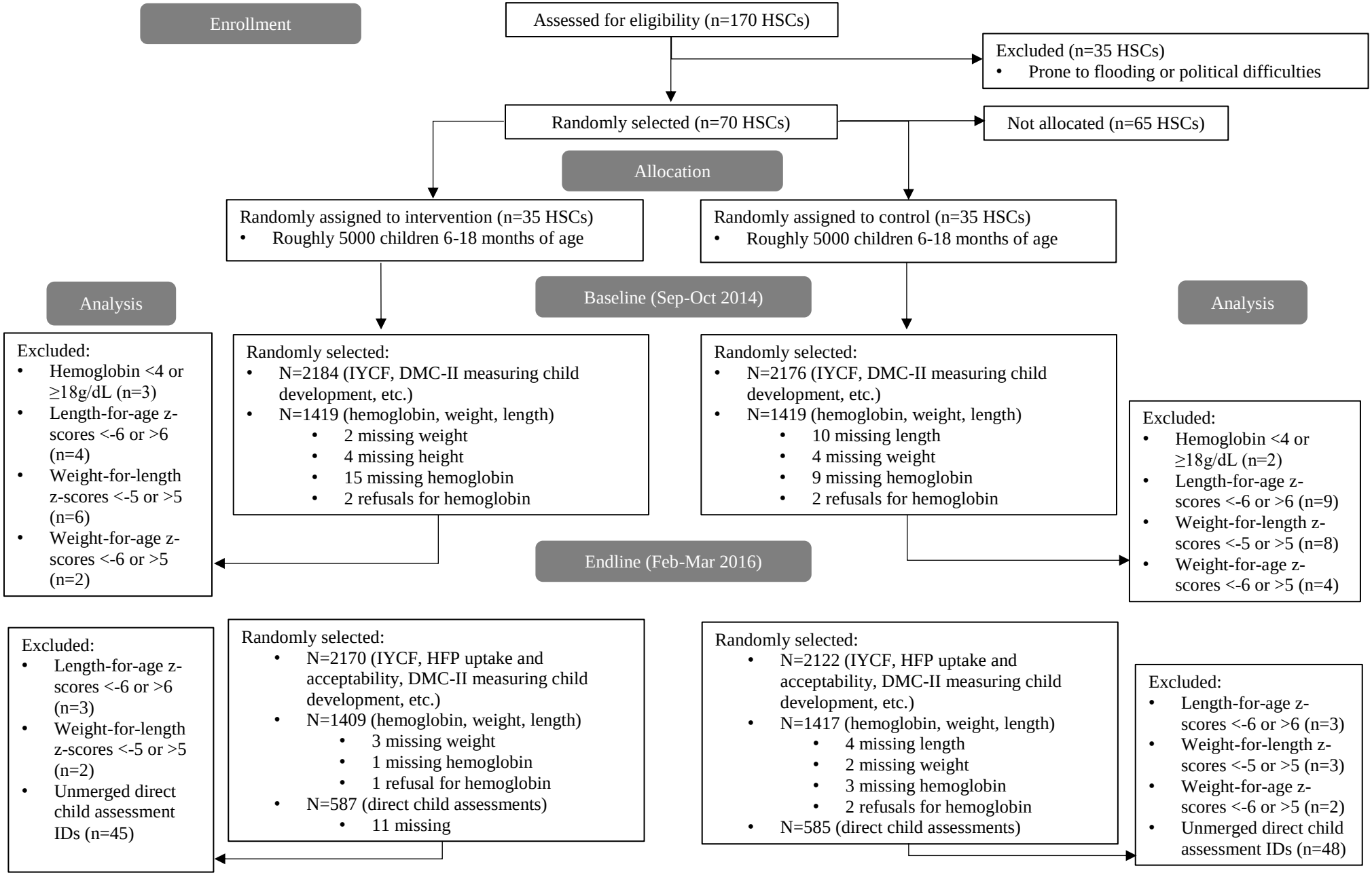
[1]All models account for clustering by Health Sub-Center and nested Anganwadi Center. Model 1 is adjusting for age of child. Model 2 is adjusting for baseline mental development scores using DMC-II, baseline hemoglobin, baseline home stimulation score, age of child, examiner, wealth index, maternal education, caste, and young mother. Ref is the reference group for the odds ration calculation. Any tolerated delay includes 3, 6, 9, and 12 seconds delay. CI, confidence interval; OR, odds ratio.
[2]Values are %(N)
[3]Values are odds ratio(95% CI)

Table 5.6: Mean scores of children 12 to 18 months of age on Elicited Imitation memory tasks by intervention group (N=1079)[1]

	Intervention[2]	**Control[2]**	**Model 1 P-value**	**Model 2 P-value**
Number of actions complete in all paradigms	4.7 ± 2.2	5.0 ± 2.0	0.43	0.13
Number of pairs of actions complete in the correct order in all paradigms	1.7 ± 1.3	1.8 ± 1.2	0.76	0.38

[1]All models account for clustering by Health Sub-Center and nested Anganwadi Center. Model 1 is adjusting for age of child. Model 2 is adjusting for baseline mental development scores using DMC-II, baseline hemoglobin, baseline home stimulation score, age of child, examiner, wealth index, maternal education, caste, and young mother. SD, standard deviation.
[2]Values are raw mean±SD.

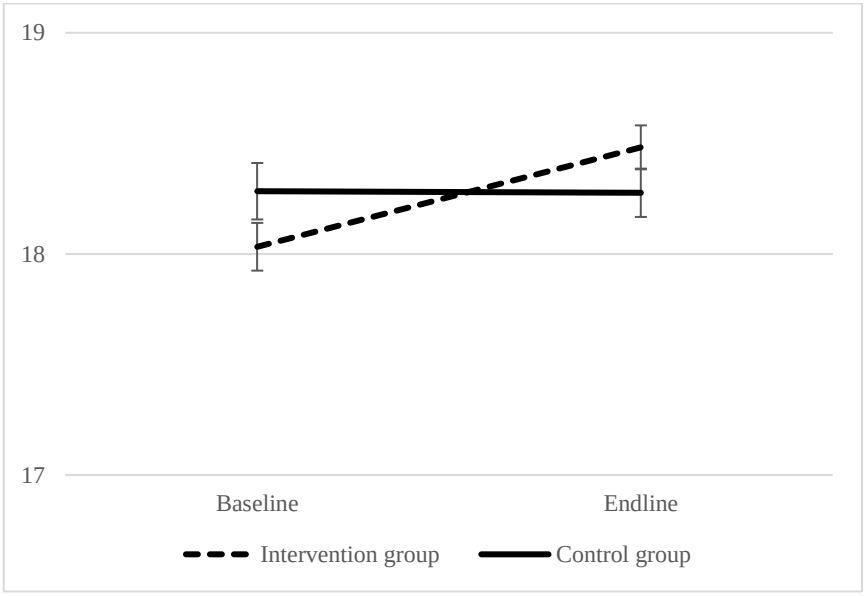
Figure 5.1: CONSORT flow diagram[1]



[1] Due to families being out-of-home during the harvest and festival season which coincided with out endline, 48 households were under-sampled for the household survey (total N=4292 at endline). At baseline and endline, 1% of children were oversampled for anthropometry (total N=2838 at baseline; 2826 at endline). At endline, 11 households were missing direct child assessments due to sickness (total N=1172). DMC-II, Developmental Milestones Checklist-II; IYCF, infant and young child feeding; HSC, health sub-center; HFP, home fortification project.

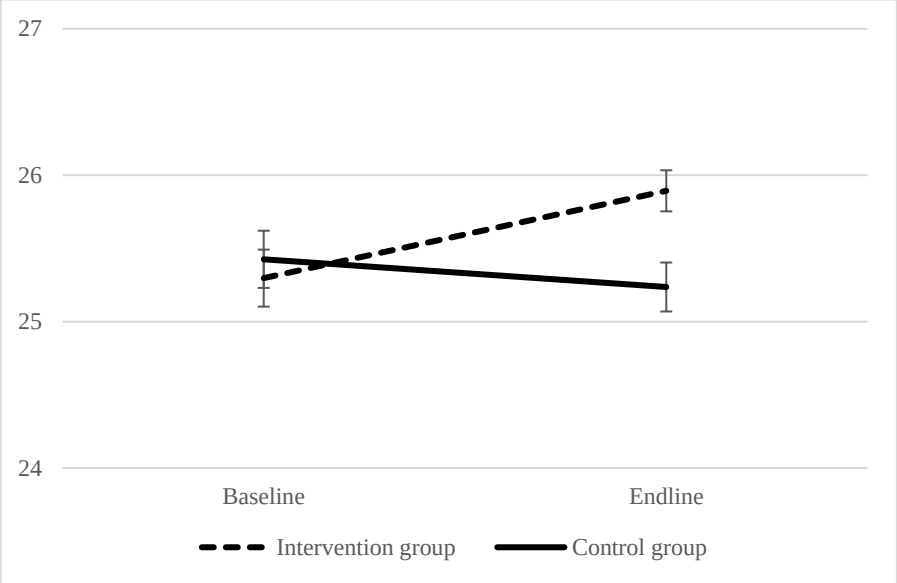
Supplemental Figure 5.1: A-not-B task sequence

Supplemental Figure 5.2: Change in motor development scores from baseline to endline in intervention and control groups[1]



[1] Point estimates are mean scores accounting for clustering by Health Sub-Center and nested Anganwadi center and adjusted for age of child, baseline hemoglobin, baseline home stimulation score, wealth index, maternal education, caste, and young mother. Error bars represent standard errors.

Supplemental Figure 5.3: Change in mental development scores from baseline to endline in intervention and control groups[1]



[1] Point estimates are mean scores accounting for clustering by Health Sub-Center and nested Anganwadi center and adjusted for age of child, baseline hemoglobin, baseline home stimulation score, wealth index, maternal education, caste, and young mother. Error bars represent standard errors.

5.8 Bridge statement 3

Findings from the effectiveness trial of home fortification with MNPs indicated a significant, but modest, effect on mental and motor development of children 6-18 months of age living in rural Bihar, India. Effect sizes ranged from 0.12-0.15. Effects were strongest for gross motor development in children 6-11 months, and for language development in children 12-18 months of age. Previous literature indicates that nutrition interventions may improve these domains at specific ages because it is when the cognitive domains are undergoing rapid development. Differences in effects by age could also be due to the measure's sensitivity to these domains at different ages. The baseline level of stimulation was identified as an important effect modifier of the impact of the intervention on both motor and mental development, wherein children from households with higher levels of stimulation improved more than children from households with lower levels of stimulation. No effects of the intervention were seen on memory or executive function. The reasons for this could not fully be explored due to the lack of baseline measures of executive function and memory. Further, longitudinal follow up data on the same children was not available, which made it difficult to examine mediators between the intervention and effects on child development. Instead, with cross-sectional data from the endline survey, Chapter 6 explores a path analysis to understand how dietary diversity, hemoglobin, LAZ, motor development, and stimulation were directly and indirectly associated with language and personal-social development, but also with memory and executive function. Using this path analysis allowed us to explore what mediators are most important. It could also clarify why effects of nutrition interventions on functional outcomes are smaller than we anticipate, and are significant for some domains but not others (i.e., language and personal-social development, but not memory and executive function).

Chapter 6: A path analysis of nutrition, stimulation, and child development among young children in Bihar, India

Larson LM[1], Martorell R[1,2], Bauer PJ[3]

1. Emory University, Doctoral Program in Nutrition and Health Sciences, Laney Graduate School, Atlanta, USA
2. Emory University, The Hubert Department of Global Health, Rollins School of Public Health, Atlanta, USA
3. Emory University, Department of Psychology, Atlanta, USA

6.1 Abstract

Nutrition plays an important role in the development of a child, particularly in low- and middle-income countries where malnutrition is often widespread. The relation between diet, hemoglobin, nutritional status, motor development, stimulation and mental development was examined in a cross-sectional sample of 1079 children 12-18 months of age living in rural Bihar, India. Path analysis revealed associations between (a) length-for-age z-scores (LAZ) and motor development (standardized β (β) = 0.285, $p<0.001$), and (b) motor and all mental development outcomes (language: β=0.422; personal-social: β=0.490; memory: β=0.139; and executive function: β=0.072, all $p<0.001$). Additionally, stimulation was significantly associated with language scores and hemoglobin concentration with memory. These findings inform interventions aimed at improving child development in Northern India.

6.2 Introduction

Infancy and early childhood are periods of additive neural development (increasing cells, neurons, synapses, etc.) and especially rapid physical and mental development. Poor nutrition during early life can have considerable and long-lasting consequences on development. The study of the relations between malnutrition and child development is critical to identifying modifiable predictors of development on which to intervene. Many studies have investigated individual associations between diet, nutritional status, stimulation, and mental development (1-4). Yet, only a few have examined the relations simultaneously (5-9). Further, a comprehensive examination of these influences has not been performed for specific cognitive functions. The current analysis adds a unique perspective by investigating a theoretical framework for how nutrition relates to memory and executive function, in addition to language and personal-social development in young children in rural Bihar, India.

Pollitt (7) hypothesized that cognitive development is influenced by nutritional status, physical growth, motor development and activity, as well as interactions among them, and between children and their social and physical environments. The study of these relations is important, particularly in low- and middle-income countries (LMICs) where many children suffer from malnutrition, poor diets, and food deprivation. One exemplar finding comes from a study of Indonesian children 12-18 months of age, in which a structural equation model of longitudinal data identified significant direct pathways between energy intake and motor activity, subsequently affecting motor and mental development (10). In a cross-sectional study of Tanzanian children 5-19 months of age, length-for-age z-score (LAZ) was associated with motor activity. In turn, motor activity was positively associated with language development and object manipulation, and negatively associated with children's tendency to fuss and time being carried (5). Associations varied by age such that LAZ and motor development, and motor and language, fussing, and object manipulation were more strongly related in older children, whereas associations between motor and carrying were stronger in younger children (5). Psychosocial

stimulation provided to the child was not measured in the study, but could play an important mediating role.

Individual associations between predictors and mental development of children are informative. Yet it is important to additionally examine the interplay between predictors and their indirect effects on development. Such examinations may be especially important in at-risk populations in which it can be expected that the multiple causes of anemia (diet, inflammation, infection, genetics, etc.), nutritional status, and motor and mental development and covariance among predictors increase the complexity of the predictive models. Interventions aimed at improving mental development in malnourished populations can use this information to target particular predictors or pathways and enhance cost-effective impact. Further, improving more than one predictor may have additive or synergistic effects on development. For example, a study in Pakistan demonstrated an additive effect of the combined delivery of nutrition supplementation and psychosocial stimulation on mental development at four years of age (11). To this point, we use structural equation modeling (SEM), a technique that allows the examination of multiple pathways simultaneously to identify both direct and indirect effects of predictors, to test a theoretical model that can also be used to inform interventions aimed at improving child development.

The study site for the current research was rural West Champaran, Bihar. Bihar is one of the poorest states in India. The latest National Family Health Survey (NFHS-4) states that 48% of children under five years of age are stunted and 64% are anemic (12). Further, over 40% of females over six years have never attended school and 42% of households do not have electricity (12). Using data from an endline evaluation of a home fortification program with multiple micronutrients in children 12-18 months of age, we used path analysis to examine the cross-sectional relations among diet, hemoglobin, nutritional status, child engagement and child development. In a significant extension of the existing literature, we used individual child behavioral measures of specific cognitive skills (memory and

executive function) as outcomes in addition to parent-reported language and personal-social development. We fitted a single model to the data, allowing for examination of multiple pathways simultaneously, as well as identification of indirect and direct effects of predictors. Moreover, we examined how the magnitude of the pathways between key determinants differed for language and personal-social development compared to memory and executive function. Key determinants in the analysis included dietary diversity, hemoglobin, LAZ, motor development, and stimulation.

6.2.1 Hypotheses for pathways of interest

Many pathways exist between nutrition and early mental development. We sampled broadly across a number of domains of function, including motor, social, and cognitive, and selected measures that, based on prior research, have been found to be predictors of these domains. Our analysis was guided by a hypothesized biopsychosocial model relating nutrient intake to mental development. The hypothesized pathways are given in **Figure 6.1**. We hypothesized an association between dietary diversity and LAZ (β_{31}) based on recent reviews and meta-analyses that have documented the effects of nutrition on linear growth in children under five years of age (13, 14). For instance, a meta-analysis of randomized controlled trials in preschool age children found a small yet significant effect of multiple micronutrients on linear growth (13). Diet (β_{41}), hemoglobin (β_{42}), and growth (β_{43}) have been shown to affect a child's level of physical activity (15) and the onset of locomotion by improving body size, proportions, mass, and strength (16, 17). Implications extend to the neurochemistry, neurotransmission, and myelination of neural pathways in the brain (18, 19). A meta-analysis of randomized trials in LMICs, Larson & Yousafzai (20) found a significant effect of multiple micronutrients on mental development (including cognitive and language abilities) (β_{61}) in children under two years of age. Further, a recent meta-analysis of preschool- and school-age children from 29 LMCIs reported a significant association between height-for-age z-scores and motor development (β_{43}), as well as cognition (overall domain), as well as motor development (4). We also hypothesized an association

among nutrient intake (β_{51}), stunting (β_{53}), and stimulation. Studies have reported that undernourished children seek more closeness with their mother and engage less often with toys compared to well-nourished children (21-24). Further, a child who is taller, appears older, and is more mobile may demand and receive more stimulation and engagement from others (25). Hemoglobin is highlighted here as a measure of the oxygen carrying capacity of blood to supply the brain and muscles, with potential to improve motor and cognitive abilities (β_{62}). Levels of iron in the brain have been shown to influence enzyme systems regulating brain growth, myelination, dopamine receptor synthesis, and energy metabolism in the hippocampus and prefrontal cortex (26-31). Lastly, diet (β_{61}), LAZ (β_{63}), motor development (β_{64}), and stimulation (β_{65}) are hypothesized to predict mental development and cognitive functioning either directly through brain development (32-34) or through a child's engagement with other people and their environment, and through attentiveness or neglect from others (35).

Our analysis uses SEM to examine a theoretical model of the associations between diet, hemoglobin, LAZ, motor development, stimulation, and an array of cognitive domains. We use a large cross-sectional sample of children 12-18 months of age living in rural Bihar, India, a population with high rates of malnutrition. Further, this is a population and age group that, to our knowledge, has not been studied on such a large scale using biological measurements of hemoglobin and LAZ in addition to measurements of social, language, executive function, and memory abilities. As such, the analysis has the potential to extend the literature by examining associations between predictors and various cognitive domains that have been tested through different means (parent report and direct child assessment) and provides the opportunity to examine multiple predictors and their interactions. Further, others have suggested that the use of more general measures of mental development in young children may be masking effects and associations between nutrition and specific cognitive domains (32). For instance, Bauer & Dugan (36) recommend extending measures of memory function, shown to be

sensitive to iron deficiency, to other nutrition research. We begin to address this gap in the literature by testing associations between nutrition-related predictors and sensitive measures of memory and executive function and comparing them to parent-reported language and personal-social development.

6.3 Methods

This study was a collaboration between CARE India and Emory University. It was reviewed and approved by the Institutional Review Boards of the 3rd Futures Group, Delhi, India, St John's Medical College & Hospital Institutional Ethics Committee, Bangalore, India, and Emory University, Atlanta, USA, and registered with the US National Institute of Health as a clinical trial (www.ClinicalTrials.gov; NCT02593136).

6.3.1 Study Design and Participants

The current analysis used data from an endline evaluation of a cluster randomized trial to examine the effects of a home fortification program with multiple micronutrient powders (MNPs) on anemia, feeding practices, and child development. A full description of the design is presented in Chapter 5. Briefly, frontline health workers delivered either MNPs and nutrition counseling (intervention) or nutrition counseling alone (control) to households with children 6-18 months of age for a period of 12 months. As part of the endline survey, conducted in February-March 2016, a household survey collected data on 2288 children 12-18 months of age from 70 rural health sub-center communities (HSCs) which had been randomly assigned to intervention or control communities using a simple randomization method with random number generator. In each HSC, 20 of the 31 children were randomly selected to be measured for anthropometry and hemoglobin; 17 of the 20 were also

tested for cognitive abilities using direct child assessments, through game-like tasks (refer to Measurements section).

6.3.2 Measurements

The data collection team included 13 supervisors, 70 household survey data collectors, 32 anthropometry/hemoglobin data collectors, and 18 research assistants for the direct child assessments. Data collectors at endline were staff from CARE India's Bihar Technical Support Program. All had at least completed secondary school and spoke the local language. Research assistants conducting direct child assessments were local university graduates in Psychology or Social Science. All data collectors and research assistants were trained in their respective duties over a two-week period. The questionnaire and direct child assessment tasks were pilot tested on mothers and children from Bihar to ensure cultural appropriateness. Training on direct child assessments was performed by the first author and a local psychologist. These individuals also monitored administration throughout data collection to ensure fidelity to the research protocol by all administrators.

Measurements of socio-demographic characteristics are described in detail in Chapter 5. A child dietary diversity score was created according to WHO guidelines, using number of food groups out of seven consumed in the past day (37). Length was measured with the Seca 417; length-for-age z-scores (LAZ) were calculated using the WHO 2006 child growth standards (38). Hemoglobin was measured with the HemoCue Hb 201+ Analyzar [HemoCue, Angelholm, Sweden] using capillary blood from a finger prick. Stimulation. Family Care Indicators (FCI), a 9-item parent-report measure, previously validated in South Asia (39), was used to assess psychosocial stimulation.

Developmental Milestones. Child development was assessed using the DMC-II (40), a 75-item parent report of gross and fine motor (32 items; e.g. "Child walks alone five steps"), language (15

items; e.g. “Child uses gestures to communicate”), and personal-social (28 items on reaction to others, recognition of others, play, dressing, eating and drinking, and toilet training) development. Motor development includes the sum of scores from the gross and fine motor subscales. Items were scored as 1 if the child had performed this activity and 0 if the child had not yet performed it. This measure has been validated in India, Burkina Faso, Kenya, and Ghana (40-44).

Memory Test. Episodic memory was measured using elicited and deferred imitation (45, 46). Three-dimensional props are used to demonstrate a specific sequence of actions that the child is then invited to imitate either immediately or after a delay. Each child was tested for immediate and delayed recall of sequences two and three steps in length. Specifically, each child was tested on one 2-step sequence and one 3-step sequence immediately after modeling (immediate recall) and one 2-step and one 3-step sequence after a delay of 10 minutes (different sequences were used to test immediate and delayed recall). Research assistants worked in pairs; one modeled the sequences and interacted with the child and the other took notes and scored the children’s performance. For a complete description of the elicited and deferred imitation task, refer to Chapter 5. To score the children’s behavior, for each sequence, we calculated a total number of individual target actions produced (hence referred to as target actions) (maximum=2 for 2-step sequences, maximum=3 for 3-step sequences) and the total number of pairs of actions produced in the target order (hence referred to as ordered recall) (maximum=1 for 2-sequence tasks, maximum=2 for 3-sequence tasks).

Executive Function. Executive function was measured using the A-not-B task (47). The child is shown a desirable object hidden under a cloth (location A), and after a brief delay, the child is allowed to search and find the object. After several successes finding the object at a particular location, the object is then hidden under a cloth at an alternate location (B). For a complete description of the A-not-B task, refer to Chapter 5. Children were scored as making an error if they reached to the empty cloth, if they did not reach at all over the course of 30 seconds, or if they reached simultaneously to both

cloths. The first reversal trial had no delay. No reversal trial was administered until the child reached correctly on the two trials prior to the reversal. Each child was given four trial attempts to retrieve the object successfully under a given delay. If the child was successful in retrieving the object on two consecutive trials, the side of hiding was changed and the delay incremented by 3 seconds. This was continued until the child failed to retrieve the object on two consecutive trials or the maximum of 12 seconds delay was successfully passed (delays: 0, 3, 6, 9, 12 seconds). To score the child's behavior, we noted perseverative error (not finding the toy under cloth B after finding toy under cloth A) and maximum tolerated delay in seconds (none, 3, 6, 9, or 12).

6.3.3 Statistical Analyses

Children 12-18 months of age were randomly selected from the full survey to receive all three developmental assessments, the DMC-II, the Elicited Imitation task, and the A-not-B test (N=1079 or 47% of the full sample). Children selected randomly for additional cognitive testing did not differ from those included in the full sample on any of the demographic or clinical characteristics. Univariate analyses were used to examine the distributions of statistical predictors and outcome variables and test for normality. Means, standard deviations, frequencies, and counts were determined for household, maternal, and child characteristics of relevance to the outcome, and the outcomes themselves. We examined the correlation matrix to identify significant correlations between exogenous and endogenous variables. Bivariate analyses informed the relations between outcomes and each statistical predictor in the hypothesized model. The model was derived from Pollitt's (7) original framework.

Univariate and bivariate analyses were conducted using SAS version 9.4 (SAS Institute; Cary, North Carolina, USA). The structural equation model was developed in MPlus version 7 (Muthén & Muthén; Los Angeles, California, USA) using weighted least square means with missing values

estimation. The hypothesized path model examined the direct and indirect associations among child dietary diversity, hemoglobin concentration, LAZ, motor development score (sum of gross and fine motor development subscales of the DMC-II), stimulation score, and language and personal-social development scores, memory, and executive function outcomes. A single model was fitted to the data.

Model fit was evaluated with common standards: a comparative fit index (CFI) (48) and a Tucker Lewis Index (TLI) (49) >0.90 for acceptable fit and >0.95 for good fit; and a root mean square error of approximation (RMSEA) (50) <0.08 for acceptable fit and <0.05 for good fit. If model fit statistics were not acceptable, modification indices were examined to decide whether additional pathways should be examined to improve model fit, and the model was re-specified.

The following variables were examined as potential covariates or confounders in our model: age of child in months, child sex, intervention group, wealth quintile of the household, parity (number of times mother has been pregnant), illness, caste, young mother (defined as <18 years of age at first birth), and maternal education (dichotomized as no vs. any school attendance). All analyses were adjusted for clustering at the HSC level. The outcomes of interest using the DMC-II test were language and personal-social development scores. Outcomes from the Elicited Imitation tasks included 1) target actions completed in all sequences (continuous), and 2) ordered recall completed in all sequences (continuous). All sequence scores were summed because there was no significant difference in the outcomes for sequences performed with or without the 10-minute delay. Outcomes of interest on the A-not-B task were 1) ability to find the object under cloth B (overcoming perseverative error), and 2) ability to tolerate 3, 6, 9, and 12 seconds, or not tolerating any delay. We grouped all children who tolerated any delay because a small proportion (22%) of children had a maximum tolerated delay between 0 and 12 seconds (i.e. maximum tolerated delay of 3, 6, or 9, seconds). The majority of children who were able to tolerate any delay were able to tolerate a 12 second delay.

Estimates for model pathways were compared to one another and significant differences were established using Wald's chi-square test.

6.4 Results

Continuous predictors and outcome variables were normally distributed. Twelve children were missing any value for the predictors of interest; all available data was used to estimate the model. No significant differences between children who had missing compared to no missing data were found for language, personal-social development, memory, executive function, maternal education, wealth quintile, age of child, sex, religion, or caste. The inter-rater reliability measurements for the DMC-II gave an average kappa coefficient of 0.96 and no single rater's kappa coefficient was below 0.70. Internal reliability estimates for the DMC-II were acceptable, with Cronbach's alpha of 0.92 for the total score, 0.88 for motor, 0.65 for language, 0.80 for personal-social, and 0.71 for cognitive subscales. Cronbach's alpha for the FCI score was 0.60, which is typical given that questions target different ways of providing stimulation and different domains of development (51).

The mean age of children was 14.6 months, and the sample included fewer girls than boys (**Table 6.1**). Almost half of children had experienced either fever, cough, or diarrhea in the two weeks prior to the survey; dietary diversity scores were low, with a mean below the acceptable minimum of four categories (Table 6.1) (37). Bivariate regression analyses indicated that dietary diversity, LAZ, stimulation score, and motor development score were significantly associated with language and personal social-development (**Table 6.2**). Hemoglobin was associated with memory and executive function scores, but dietary diversity and stimulation were not (Table 6.2). Although dietary diversity and stimulation were not associated with these specific cognitive functions in bivariate analyses, they

were included in the modeling effort (see below) due to their theoretical significance. Child age in months, household wealth quintile, maternal education, child sex, religion, and caste were identified as potential confounders because they were significantly associated with at least one outcome and predictive variable. The magnitude of the associations did not differ significantly before and after adjustment for confounding variables. The correlation matrix shows that language and personal-social development scores were highly inter-correlated, as was motor development with language, personal-social development, memory, and LAZ (**Table 6.3**).

The model fit statistics confirmed the data fit the model (CFI=1.000, TLI=1.076, RMSEA<0.001). The model indicated no significant association between dietary diversity and any endogenous variables (hemoglobin, LAZ, motor development, stimulation, or any development outcomes) (**Figures 6.2-6.7**). LAZ was moderately and significantly associated with motor development (standardized β (β) = 0.285, p<0.001); hemoglobin was modestly associated with motor development (β=0.053, p=0.046); and motor development was modestly associated with stimulation (β=0.097, p=0.029) (Figures 6.2-6.7). Motor development was strongly and significantly associated with language development (β=0.422, p<0.001) (Figure 6.1) and with personal-social development (β=0.490, p<0.001) (Figure 6.3). Motor development was moderately associated with memory scores and executive function scores (Figures 6.4-6.7). The associations between motor and language and between motor and personal-social scores were significantly larger than the associations between motor and memory and between motor and executive function scores (Wald test p<0.001 for all). Stimulation was significantly associated with language development (Figure 6.2); this association was significantly smaller than the association between motor and language development, but larger than the association between LAZ and language development (Wald test p<0.001 for all). Out of all the child development outcomes, hemoglobin was significantly associated with only the memory outcome of ordered recall.

Significant indirect effects were observed for hemoglobin on motor, language, personal social, and memory (target actions) score (**Supplemental Tables 6.1 & 6.2**). Significant indirect effects were observed for LAZ on stimulation, language, personal-social, and memory scores (Supplemental Tables 6.1 & 6.2). R^2 values are shown (**Supplemental Table 6.3**).

6.5 Discussion

Our findings contribute to the literature by examining nutritional and psychosocial predictors of language and personal-social development, in addition to memory and executive function, in an understudied population and age group. The current path analysis examined direct and indirect associations between nutrient intake, biological markers, and child engagement, and outcomes of language, personal-social development, memory, and executive function in children 12-18 months of age living in rural Bihar. The framework used was adapted from Pollitt's (7) work to include hemoglobin and examine differences in the pathways for a range of cognitive outcomes, controlling for age and other confounding variables. The significant associations between LAZ, hemoglobin, motor, stimulation, and cognitive outcomes add to previous models by examining associations with parental report measures of development, as well as behavioral measures of specific cognitive functions.

The strongest and most consistent pattern observed was the direct and indirect relation between LAZ, motor development and mental development, including personal-social development, memory, and executive function, but especially language development. Similar significant associations between LAZ and motor development, and LAZ and language development, have been reported in a study of children 5-19 months of age living in Zanzibar (5). Direct associations between linear growth and motor and language development have also been reported in a study of children from Ghana, Malawi, and Burkina Faso (8). Strength, muscle mass, and endurance are important in children 6 to 24 months

of age who are learning to crawl, walk, and run (52). Additionally, a child who appears older may be engaged by their parents and adults more often and with more stimulating language than a child who looks younger. Importantly, the benefits of motor development on mental development accrue only if they lead to richer experiences, more objects to play with, and stimulating situations and interactions with others (both gross and fine motor abilities) (16). This may depend on the type of nutrition provided. For instance, Aburto et al found that child supplementation for 4 months with macro- and micronutrients enhanced the level of exploration (i.e., touching and manipulation of objects, fine motor abilities), whereas supplementation with only multiple micronutrients increased the level of activity performed (i.e., gross motor movements) (53). The differences Aburto et al (53) captured could be due, in part, to their use of direct observation measurements of children's motor development, a concept which should be considered in future mediation analyses.

An association often noted (45, 54) and reinforced in our study is the relation between stimulation and mental development; however, in our case, it is confined to language development. The type of stimulation assessed (i.e. reading and play materials available, interaction, singing, and story-telling with others, and time spent naming, counting, etc.) may be less relevant to memory and executive function. Motor development is presented in our study as a predictor of level of child stimulation with the understanding that a child's mobility and fine movements may improve the amount and quality of stimulation provided. Yet, the reverse association may also be applicable, in that children who are given more stimulating material will have more opportunity to develop their motor skills (particularly object manipulation).

A weak, but significant, direct or indirect (through motor development) association with hemoglobin was observed for language, personal-social development, and memory. Others have also reported significant associations between hemoglobin and motor development (5, 6, 8). Research in Chilean children showed that greater severity of anemia and duration of anemia of more than 3 months

was associated with decreased psychomotor development scores (55). Anemia in children can cause lethargy, reduced attention, and reduced responsiveness to peers resulting in fewer interactions and slower exploration of their environment (55, 56). Similar to our findings, no significant association was seen between hemoglobin and language development in Zanzibari children (5, 6). On the other hand, a combined analysis of children from three African countries reported significant associations between hemoglobin at 6 months of age, as well as hemoglobin change from 6 to 18 months of age, and language development at 18 months of age (8). The measurement of language development in two of the three countries was performed using a parent-reported 100-word vocabulary checklist (8), different than the DMC-II used in this study which also includes measures of receptive language.

There was no evidence in our study for an association between diet and LAZ or hemoglobin, which could be a function of the dietary diversity being a relatively rough measure of nutrient intake, only examining food groups consumed in the past 24 hours. Dietary intake can vary between seasons in rural Bihar, and may not reflect the longer term influences on linear growth. Findings were similar when using only animal source foods as the predictor (data not shown). The lack of association could also be due to the role of infection (not measured here) and its effect on growth and nutritional biomarkers (57).

Our study demonstrates two important findings with respect to memory: hemoglobin concentration is an important statistical predictor of memory (more so than for general cognitive abilities and executive function), and ordered recall in the elicited and deferred imitation task may be a more sensitive measure of memory than the number of target actions completed. Others have found similar relations between hemoglobin and memory (58-61). For instance, Eilander et al (60) reported that hemoglobin was positively associated with memory in Indian school-age children. The associations observed could be due to the effects of cerebral blood flow (62) and improved function of areas of the brain important for memory (the hippocampus, cerebral cortex, and striatum) (63, 64). A

study of infants of diabetic mothers, exposed to hypoxic conditions and iron deficiency prenatally, showed decreased recall abilities at one year of age compared to children of non-diabetic mothers using the elicited and deferred imitation task (65). Similar to our findings, differences were observed in ordered recall but not target actions. As in Riggins et al (65), we argue that the specificity of the relation reflects the greater memory demand imposed when reproducing an ordered sequence of actions in the absence of perceptual support, versus performing individual actions that are cued by the objects on which they are performed. In the present research, infants' performance at immediate and delayed recall did not differ. In contrast, in Riggins et al (65), for infants of diabetic mothers, ordered recall was significantly lower at delayed recall than at immediate recall, a finding attributed to likely hippocampal impairment in the sample (66). Consistent with this suggestion, delayed recall at one year was marginally correlated with newborn ferritin concentrations (65). Iron deficiency is an important risk factor for anemia in our population (67) and may contribute to the relation observed with memory.

The only significant association with executive function was motor development. Other nutrition trials, published after the completion of our study, have shown a similar lack of relation with nutrition as measured using the A-not-B task in this same age group (68, 69). The A-not-B task has been shown to be sensitive to poverty (70) and other health exposures, such as phenylketonuria (71) and maternal drug abuse during pregnancy (72). However, aspects of executive function measured by the A-not-B task may not be the ones that are impacted by nutrition at this particular point in development. Benefits of nutrition on executive function as measured here may become more apparent later in life when areas of the brain (especially the prefrontal cortex) develop more fully (73).

Limitations of this analysis include the cross-sectional nature of the associations. The relations observed cannot be taken as causal, and as mentioned, the direction of some associations presented could be reversed. Dietary diversity is a rough measure of food groups consumed over the previous day, and does not approximate nutrient or food intake. Further, the inclusion of other nutritional and

infection biomarker measurements, such as ferritin, C-reactive protein, and alpha1-acid-glycoprotein, or information on breastfeeding initiation and duration may have strengthened our model. Lastly, measurement of motor, language, and personal-social development were parent-reported and could be biased by the respondent.

On the other hand, memory and executive function were measured through interactions with the children themselves which would minimize caretaker bias. Other strengths of the study include a large sample size, rigorous sampling of an at-risk population, and the measurement of a range of child development outcomes. To our knowledge, this is the first study to use the elicited and deferred imitation task to examine memory in young children living in South Asia.

In conclusion, our findings inform the development of children in this population, and could contribute to the design of interventions to improve child development in this context. A path analysis examined the relations between nutrient intake, biological markers and child engagement and parental report measures of general cognitive function, as well as behavioral measures of memory and executive function. The strong direct and indirect relations observed between LAZ, motor development and cognitive abilities highlights their important influence in this population. Stimulation has a significant association with language development, as does hemoglobin with memory. Therefore, nutrition interventions targeting children under two years of age aimed at improving growth and hemoglobin could additionally have beneficial effects on child development.

6.6 Acknowledgements

We wish to thank Regine Haardoerfer for her contributions to the analysis, Indrajit Chaudhuri, Rukshan Mehta, Usha Ramakrishnan, Sridhar Srikantiah, Amy Webb Girard, and Melissa Young for their contributions to the design and implementation of the larger study, and our collaborators, CARE

India, as well as the women and children who participated in this study. Finally, we wish to thank the Laney Graduate School at Emory University for supporting L.M.L as she pursues her PhD.

6.7 Chapter 6 references

1. Barros AJ, Matijasevich A, Santos IS, Halpern R. Child development in a birth cohort: effect of child stimulation is stronger in less educated mothers. International journal of epidemiology 2010;39(1):285-94. doi: 10.1093/ije/dyp272.
2. Hadley C, Tegegn A, Tessema F, Asefa M, Galea S. Parental symptoms of common mental disorders and children's social, motor, and language development in sub-Saharan Africa. Annals of human biology 2008;35(3):259-75. doi: 10.1080/03014460802043624.
3. Servili C, Medhin G, Hanlon C, Tomlinson M, Worku B, Baheretibeb Y, Dewey M, Alem A, Prince M. Maternal common mental disorders and infant development in Ethiopia: the P-MaMiE Birth Cohort. BMC public health 2010;10:693. doi: 10.1186/1471-2458-10-693.
4. Sudfeld CR, McCoy DC, Danaei G, Fink G, Ezzati M, Andrews KG, Fawzi WW. Linear growth and child development in low- and middle-income countries: a meta-analysis. Pediatrics 2015;135(5):e1266-75. doi: 10.1542/peds.2014-3111.
5. Olney DK, Kariger PK, Stoltzfus RJ, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Pollitt E. Development of nutritionally at-risk young children is predicted by malaria, anemia, and stunting in Pemba, Zanzibar. The Journal of nutrition 2009;139(4):763-72. doi: 10.3945/jn.107.086231.
6. Olney DK, Kariger PK, Stoltzfus RJ, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Pollitt E. Developmental effects of micronutrient supplementation and malaria in Zanzibari children. Early human development 2013;89(9):667-74. doi: 10.1016/j.earlhumdev.2013.04.013.
7. Pollitt E. A developmental view of the undernourished child: background and purpose of the study in Pangalengan, Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S2-10.
8. Prado EL, Abbeddou S, Adu-Afarwuah S, Arimond M, Ashorn P, Ashorn U, Bendabenda J, Brown KH, Hess SY, Kortekangas E, et al. Predictors and pathways of language and motor development in four prospective cohorts of young children in Ghana, Malawi, and Burkina Faso. Journal of child psychology and psychiatry, and allied disciplines 2017. doi: 10.1111/jcpp.12751.
9. Walka H, Pollitt E. A preliminary test of a developmental model for the study of undernourished children in Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S21-7.
10. Pollitt E, Jahari A, Walka H. A developmental view of the effects of an energy and micronutrient supplement in undernourished children in Indonesia. European journal of clinical nutrition 2000;54 Suppl 2:S107-13.
11. Yousafzai AK, Obradovic J, Rasheed MA, Rizvi A, Portilla XA, Tirado-Strayer N, Siyal S, Memon U. 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. The Lancet Global health 2016;4(8):e548-58. doi: 10.1016/s2214-109x(16)30100-0.
12. International Institute of Population Sciences. NFHS-4 (National Family Health Survey-4) 2015-16: State Fact Sheet Bihar. 2016.
13. Ramakrishnan U, Nguyen P, Martorell R. Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions. The American journal of clinical nutrition 2009;89(1):191-203. doi: 10.3945/ajcn.2008.26862.
14. Roberts JL, Stein AD. The Impact of Nutritional Interventions beyond the First 2 Years of Life on Linear Growth: A Systematic Review and Meta-Analysis. Advances in nutrition (Bethesda, Md) 2017;8(2):323-36. doi: 10.3945/an.116.013938.

15. Meeks Gardner J, Grantham-McGregor SM, Chang SM, Himes JH, Powell CA. Activity and behavioral development in stunted and nonstunted children and response to nutritional supplementation. Child development 1995;66(6):1785-97.
16. Adolph KE, Tamis-LeMonda CS. The Costs and Benefits of Development: The Transition From Crawling to Walking. Child Dev Perspect 2014;8(4):187-92. doi: 10.1111/cdep.12085.
17. Thelen E. Developmental origins of motor coordination: leg movements in human infants. Developmental psychobiology 1985;18(1):1-22. doi: 10.1002/dev.420180102.
18. Forssberg H. Ontogeny of human locomotor control. I. Infant stepping, supported locomotion and transition to independent locomotion. Experimental brain research 1985;57(3):480-93.
19. Pollitt E, Husaini MA, Harahap H, Halati S, Nugraheni A, Sherlock AO. Stunting and delayed motor development in rural West Java. American Journal of Human Biology 1994;6(5):627-35.
20. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children under-two in low- and middle-income countries. Maternal & child nutrition 2017;13(1). doi: 10.1111/mcn.12229.
21. Lozoff B, Klein NK, Nelson EC, McClish DK, Manuel M, Chacon ME. Behavior of infants with iron-deficiency anemia. Child development 1998;69(1):24-36.
22. Graves P. Nutrition and infant behavior: a replication study in the Katmandu Valley, Nepal. The American journal of clinical nutrition 1978;31(3):541-51.
23. Wachs TD, Sigman M, Bishry Z, Moussa W, Jerome N, Neumann C, Bwibo N, McDonald MA. Caregiver child interaction patterns in two cultures in relation to nutritional intake. International Journal of Behavioral Development 1992;15(1):1-18.
24. Sigman M, Wachs TD. Structure, Continuity, and Nutritional Correlates of Caregiver Behavior. Cultural approaches to parenting 1991:123.
25. Brown JL, Pollitt E. Malnutrition, poverty and intellectual development. Scientific American 1996;274(2):38-43.
26. de Ungria M, Rao R, Wobken JD, Luciana M, Nelson CA, Georgieff MK. Perinatal iron deficiency decreases cytochrome c oxidase (CytOx) activity in selected regions of neonatal rat brain. Pediatric research 2000;48(2):169-76. doi: 10.1203/00006450-200008000-00009.
27. Lozoff B. Perinatal iron deficiency and the developing brain. Pediatric research 2000;48(2):137-9. doi: 10.1203/00006450-200008000-00003.
28. Beard J. Iron deficiency alters brain development and functioning. The Journal of nutrition 2003;133(5 Suppl 1):1468s-72s.
29. Rao R, Tkac I, Schmidt AT, Georgieff MK. Fetal and neonatal iron deficiency causes volume loss and alters the neurochemical profile of the adult rat hippocampus. Nutritional neuroscience 2011;14(2):59-65. doi: 10.1179/1476830511y.0000000001.
30. Larkin EC, Jarratt BA, Rao GA. Reduction of relative levels of nervonic to lignoceric acid in the brain of rat pups due to iron deficiency. Nutrition Research 1986;6(3):309-17.
31. Erikson KM, Pinero DJ, Connor JR, Beard JL. Regional brain iron, ferritin and transferrin concentrations during iron deficiency and iron repletion in developing rats. The Journal of nutrition 1997;127(10):2030-8.
32. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. The American journal of clinical nutrition 2007;85(2):614s-20s.
33. Higley JD, Suomi SJ, Linnoila M. A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. Biological psychiatry 1992;32(2):127-45.
34. Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. Proceedings of the National Academy of Sciences 1998;95(9):5335-40.

35. Cheatham CL, Larkina M, Bauer PJ, Toth SL, Cicchetti D. Declarative memory in abused and neglected infants. Advances in child development and behavior 2010;38:161-82.
36. Bauer PJ, Dugan JA. Suggested use of sensitive measures of memory to detect functional effects of maternal iodine supplementation on hippocampal development. The American journal of clinical nutrition 2016;104 Suppl 3:935s-40s. doi: 10.3945/ajcn.115.110437.
37. WHO. Indicators for assessing infant and young child feeding practices: part 1: definitions. Geneva. http://apps.who.int/iris/bitstream/10665/43895/1/9789241596664_eng.pdf: World Health Organization, 2008.
38. de Onis M, Onyango AW, Van den Broeck J, Chumlea WC, Martorell R. Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference. Food and nutrition bulletin 2004;25(1 Suppl):S27-36.
39. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. Journal of health, population, and nutrition 2010;28(1):23.
40. Prado EL, Abubakar AA, Abbeddou S, Jimenez EY, Some JW, Ouedraogo JB. Extending the Developmental Milestones Checklist for use in a different context in Sub-Saharan Africa. Acta paediatrica (Oslo, Norway : 1992) 2014;103(4):447-54. doi: 10.1111/apa.12540.
41. Larson LM, Young MF, Ramakrishnan U, Webb Girard A, Verma P, Chaudhuri I, Srikantiah S, Martorell R. A Cross-Sectional Survey in Rural Bihar, India, Indicates That Nutritional Status, Diet, and Stimulation Are Associated with Motor and Mental Development in Young Children. The Journal of nutrition 2017;147(8):1578-85. doi: 10.3945/jn.117.251231.
42. Prado EL, Abbeddou S, Yakes Jimenez E, Some JW, Ouedraogo ZP, Vosti SA, Dewey KG, Brown KH, Hess SY, Ouedraogo JB. Lipid-Based Nutrient Supplements Plus Malaria and Diarrhea Treatment Increase Infant Development Scores in a Cluster-Randomized Trial in Burkina Faso. The Journal of nutrition 2016. doi: 10.3945/jn.115.225524.
43. Abubakar A, Holding P, Van de Vijver F, Bomu G, Van Baar A. Developmental monitoring using caregiver reports in a resource-limited setting: the case of Kilifi, Kenya. Acta paediatrica (Oslo, Norway : 1992) 2010;99(2):291-7. doi: 10.1111/j.1651-2227.2009.01561.x.
44. Ahun M. Maternal and child health and development in rural Ghana. Department of Psychology. Montreal, Quebec: McGill University, 2015.
45. Bauer PJ. Declarative memory in infancy: an introduction to typical and atypical development. Advances in child development and behavior 2010;38:1-25.
46. Bauer PJ. New developments in the study of infant memory. Handbook of research methods in developmental science 2005:467-88.
47. Diamond A. Development of the ability to use recall to guide action, as indicated by infants' performance on AB. Child development 1985;56(4):868-83.
48. Bentler PM. Comparative fit indexes in structural models. Psychological bulletin 1990;107(2):238-46.
49. Tucker LR, Lewis C. A reliability coefficient for maximum likelihood factor analysis. Psychometrika 1973;38(1):1-10.
50. Steiger JH. Structural model evaluation and modification: An interval estimation approach. Multivariate behavioral research 1990;25(2):173-80.
51. Bornstein MH, Putnick DL, Lansford JE, Deater-Deckard K, Bradley RH. A Developmental Analysis of Caregiving Modalities Across Infancy in 38 Low- and Middle-Income Countries. Child development 2015;86(5):1571-87. doi: 10.1111/cdev.12402.
52. Adolph KE, Vereijken B, Denny MA. Learning to crawl. Child development 1998;69(5):1299-312.

53. Aburto NJ, Ramirez-Zea M, Neufeld LM, Flores-Ayala R. The effect of nutritional supplementation on physical activity and exploratory behavior of Mexican infants aged 8-12 months. European journal of clinical nutrition 2010;64(6):644-51. doi: 10.1038/ejcn.2010.52.
54. Hamadani JD, Huda SN, Khatun F, Grantham-McGregor SM. Psychosocial stimulation improves the development of undernourished children in rural Bangladesh. The Journal of nutrition 2006;136(10):2645-52.
55. Walter T. Infancy: mental and motor development. The American journal of clinical nutrition 1989;50(3):655-66.
56. Black MM, Quigg AM, Hurley KM, Pepper MR. Iron deficiency and iron-deficiency anemia in the first two years of life: strategies to prevent loss of developmental potential. Nutr Rev 2011;69 Suppl 1:S64-70. doi: 10.1111/j.1753-4887.2011.00435.x.
57. Namaste SM, Aaron GJ, Varadhan R, Peerson JM, Suchdev PS. Methodologic approach for the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. The American journal of clinical nutrition 2017. doi: 10.3945/ajcn.116.142273.
58. Riggins T, Miller N, Bauer P, Georgieff M, Nelson C. Consequences of maternal diabetes mellitus and neonatal iron status on children's explicit memory performance. Developmental neuropsychology 2009;34(6):762-79.
59. DeBoer T, Wewerka S, Bauer PJ, Georgieff MK, Nelson CA. Explicit memory performance in infants of diabetic mothers at 1 year of age. Developmental medicine and child neurology 2005;47(8):525-31.
60. Eilander A, Muthayya S, van der Knaap H, Srinivasan K, Thomas T, Kok FJ, Kurpad AV, Osendarp SJ. Undernutrition, fatty acid and micronutrient status in relation to cognitive performance in Indian school children: a cross-sectional study. The British journal of nutrition 2010;103(7):1056-64. doi: 10.1017/s000711450999273x.
61. Virues-Ortega J, Bucks R, Kirkham FJ, Baldeweg T, Baya-Botti A, Hogan AM. Changing patterns of neuropsychological functioning in children living at high altitude above and below 4000 m: a report from the Bolivian Children Living at Altitude (BoCLA) study. Dev Sci 2011;14(5):1185-93. doi: 10.1111/j.1467-7687.2011.01064.x.
62. Hill CM, Hogan AM, Onugha N, Harrison D, Cooper S, McGrigor VJ, Datta A, Kirkham FJ. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. Pediatrics 2006;118(4):e1100-8. doi: 10.1542/peds.2006-0092.
63. Nelson C, Silverstein FS. Acute disruption of cytochrome oxidase activity in brain in a perinatal rat stroke model. Pediatric research 1994;36(1 Pt 1):12-9. doi: 10.1203/00006450-199407001-00003.
64. McDonough L, Mandler JM, McKee RD, Squire LR. The deferred imitation task as a nonverbal measure of declarative memory. Proceedings of the National Academy of Sciences of the United States of America 1995;92(16):7580-4.
65. Riggins T, Bauer PJ, Georgieff MK, Nelson CA. Declarative memory performance in infants of diabetic mothers. Advances in child development and behavior 2010;38:73-110.
66. Reed JM, Squire LR. Retrograde amnesia for facts and events: findings from four new cases. Journal of Neuroscience 1998;18(10):3943-54.
67. Kumar T, Taneja S, Yajnik CS, Bhandari N, Strand TA. Prevalence and predictors of anemia in a population of North Indian children. Nutrition (Burbank, Los Angeles County, Calif) 2014;30(5):531-7. doi: 10.1016/j.nut.2013.09.015.
68. Prado EL, Maleta K, Ashorn P, Ashorn U, Vosti SA, Sadalaki J, Dewey KG. Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial

in Malawi. The American journal of clinical nutrition 2016;103(3):784-93. doi: 10.3945/ajcn.115.114579.

69. Matias SL, Mridha MK, Tofail F, Arnold CD, Khan MS, Siddiqui Z, Ullah MB, Dewey KG. Home fortification during the first 1000 d improves child development in Bangladesh: a cluster-randomized effectiveness trial. The American journal of clinical nutrition 2017. doi: 10.3945/ajcn.116.150318.
70. Lipina SJ, Martelli MI, Vuelta B, Colombo JA. Performance on the A-not-B task of Argentinean infants from unsatisfied and satisfied basic needs homes. Interamerican Journal of Psychology 2005;39(1):49.
71. Diamond A, Prevor MB, Callender G, Druin DP. Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. Monographs of the Society for Research in Child Development 1997;62(4):i-v, 1-208.
72. Noland JS, Singer LT, Mehta SK, Super DM. Prenatal cocaine/polydrug exposure and infant performance on an executive functioning task. Developmental neuropsychology 2003;24(1):499-517. doi: 10.1207/s15326942dn2401_05.
73. Diamond A, Ling DS. Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. Developmental cognitive neuroscience 2016;18:34-48. doi: 10.1016/j.dcn.2015.11.005.

Table 6.1: Demographic and clinical characteristics of children 12-18 months of age with measures of child development (N=1079)[1]

	Children 12-18 months of age
Age of child in months	14.6 ± 1.7
Multiple micronutrient powder (MNP) assignment	50.2 (542)
Girls	48.1 (519)
Maternal education	
Any schooling	43.1 (465)
Parity	2.7 ± 1.7
Young mother	60.6 (653)
Religion	
Hindu	79.3 (844)
Muslim	21.7 (234)
Caste	
Scheduled caste	20.9 (226)
Scheduled tribe	9.2 (99)
Other backwards caste	10.6 (114)
Household wealth index (quintile)	3.0 ± 1.4
Recent illness	
Any	48.3 (521)
Fever	32.9 (355)
Cough	35.8 (386)
Diarrhea	11.6 (125)
Child nutrition and engagement	
Dietary diversity score (out of 7)	3.4 ± 1.2
Family Care Indicators score (out of 9)	5.6 ± 1.7
Hemoglobin concentration (g/dL)	10.4 ± 1.3
Length-for-age z-score	-1.7 ± 1.1
Child development:	

Motor development score (out of 32)	23.4 ± 4.2
Language development score (out of 15)	6.7 ± 2.1
Personal-social development score (out of 28)	18.8 ± 2.8
Memory score (ordered recall) (out of 6)	1.8 ± 1.2
Memory score (target actions) (out of 10)	5.0 ± 1.9
Overcame perseverative error	69.5 (742)
Any tolerated delay	59.6 (636)

[1] Values are % (N) or mean ± SD. All estimates account for cluster-randomization by Health Sub-Center. CI, confidence interval; SD, standard deviation.

Table 6.2: Bivariate analyses examining predictors of language, personal-social, memory, and executive function[1]

	Unadjusted	P-value	Adjusted	P-value
Language development score				
Dietary diversity	0.10 (-0.03, 0.23)	0.138	0.05 (-0.05, 0.15)	0.315
Hemoglobin	0.17 (0.06, 0.28)	0.003	0.12 (0.01, 0.22)	0.035
Length-for-age z-score	0.34 (0.20, 0.48)	<0.001	0.37 (0.24, 0.50)	<0.001
Motor development score	0.29 (0.26, 0.31)	<0.001	0.23 (0.20, 0.27)	<0.001
Stimulation score	0.31 (0.22, 0.39)	<0.001	0.24 (0.15, 0.32)	<0.001
Personal-social development score				
Dietary diversity	0.16 (0.01, 0.32)	0.040	0.11 (-0.01, 0.23)	0.082
Hemoglobin	0.10 (-0.03, 0.24)	0.125	0.04 (-0.09, 0.16)	0.559
Length-for-age z-score	0.41 (0.23, 0.59)	<0.001	0.44 (0.27, 0.60)	<0.001
Motor development score	0.38 (0.35, 0.41)	<0.001	0.33 (0.29, 0.37)	<0.001
Stimulation score	0.24 (0.14, 0.34)	<0.001	0.14 (0.03, 0.24)	0.012
Memory score (ordered recall)				
Dietary diversity	0.01 (-0.07, 0.09)	0.859	0.00 (-0.08, 0.07)	0.921
Hemoglobin	0.10 (0.04, 0.15)	0.001	0.07 (0.03, 0.12)	0.004
Length-for-age z-score	0.09 (0.01, 0.16)	0.026	0.10 (0.02, 0.17)	0.011
Motor development score	0.07 (0.06, 0.09)	<0.001	0.04 (0.03, 0.06)	<0.001
Stimulation score	0.01 (-0.04, 0.06)	0.742	-0.02 (-0.07, 0.03)	0.343
Memory score (target actions)				
Dietary diversity	0.02 (-0.10, 0.15)	0.701	0.01 (-0.12, 0.13)	0.928
Hemoglobin	0.11 (0.01, 0.20)	0.036	0.08 (-0.01, 0.18)	0.076
Length-for-age z-score	0.13 (0.01, 0.26)	0.034	0.14 (0.02, 0.26)	0.019
Motor development score	0.12 (0.09, 0.15)	<0.001	0.09 (0.06, 0.12)	<0.001
Stimulation score	0.06 (-0.02, 0.15)	0.136	0.02 (-0.07, 0.11)	0.628
Executive function score (overcome perseverative error)				
Dietary diversity	0.01 (-0.02, 0.04)	0.398	0.01 (-0.02, 0.04)	0.411
Hemoglobin	0.02 (0.00, 0.05)	0.021	0.02 (0.00, 0.04)	0.028

Length-for-age z-score	0.01 (-0.01, 0.04)	0.273	0.01 (-0.01, 0.04)	0.307
Motor development score	0.01 (0.01, 0.02)	0.001	0.01 (0.00, 0.01)	0.048
Stimulation score	0.02 (0.00, 0.03)	0.062	0.01 (-0.01, 0.03)	0.165
Executive function score (any tolerated delay)				
Dietary diversity	0.01 (-0.02, 0.04)	0.514	0.01 (-0.02, 0.04)	0.482
Hemoglobin	0.03 (0.00, 0.05)	0.040	0.02 (0.00, 0.04)	0.092
Length-for-age z-score	0.03 (0.00, 0.05)	0.048	0.02 (-0.01, 0.04)	0.126
Motor development score	0.01 (0.00, 0.02)	0.001	0.01 (0.00, 0.01)	0.084
Stimulation score	0.01 (-0.01, 0.03)	0.180	0.00 (-0.02, 0.03)	0.624

1 Values are β coefficients (95% CI). All adjusted for clustering at the health sub-center level. Adjusted analyses accounting for age of child in months, child sex, intervention group, wealth quintile of the household, religion, caste, and maternal education.

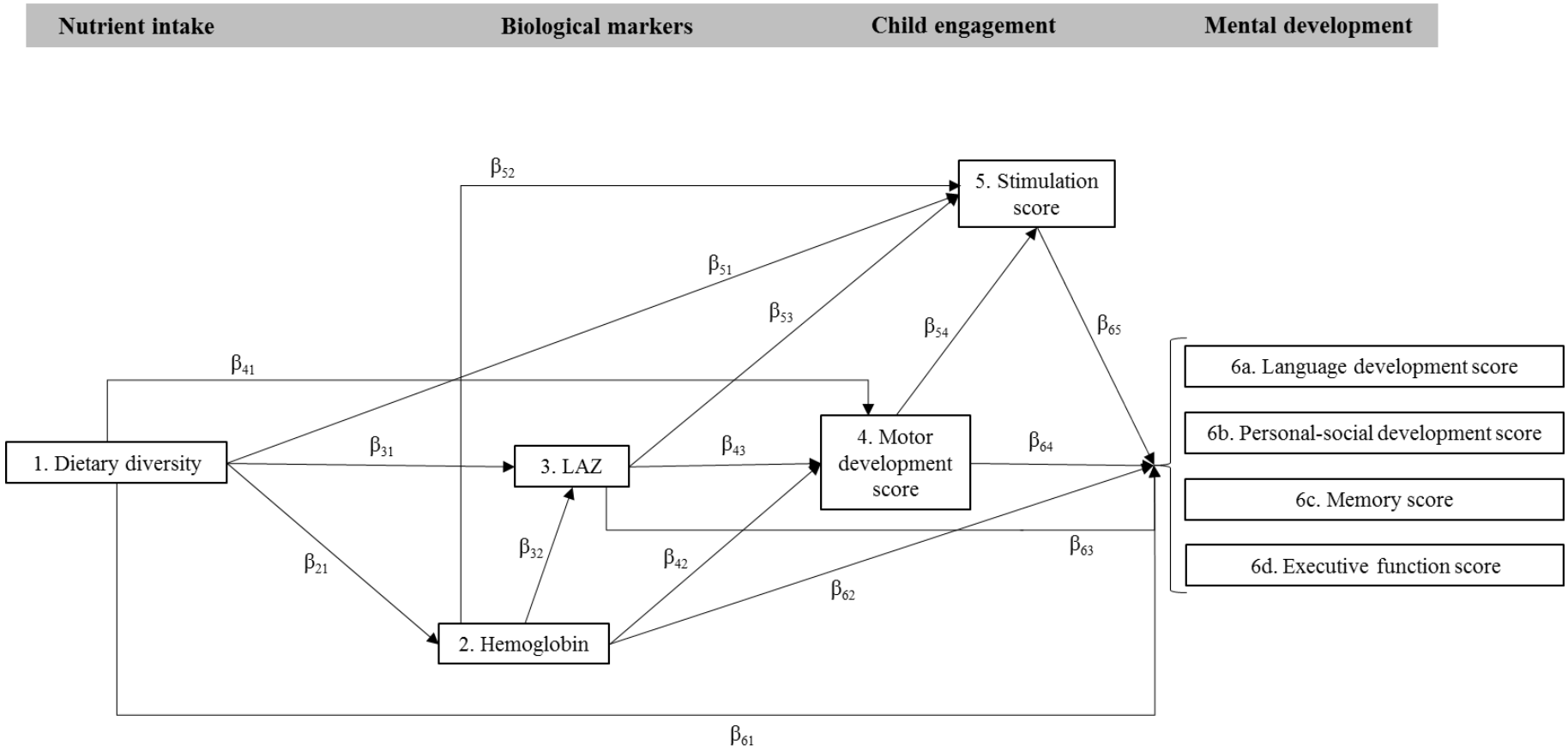
Table 6.3: Correlation matrix between predictors and mental development[1]

	Personal-social development	Executive function (overcome perseverative error)	Executive function (tolerate any delay)	Memory (target actions)	Memory (ordered recall)	Dietary diversity score	Hemoglobin concentration	Length-for-age z-score	Stimulation score	Motor development
Language development	0.60 (<0.0001)	0.06 (0.0518)	0.08 (0.0142)	0.20 (<0.0001)	0.22 (<0.0001)	0.05 (0.0825)	0.11 (0.0006)	0.18 (<0.0001)	0.24 (<0.0001)	0.56 (<0.0001)
Personal-social development		0.05 (0.1228)	0.07 (0.0218)	0.20 (<0.0001)	0.19 (<0.0001)	0.07 (0.0259)	0.05 (0.0959)	0.17 (<0.0001)	0.15 (<0.0001)	0.58 (<0.0001)
Executive function (overcome perseverative error)			0.79 (<0.0001)	0.30 (<0.0001)	0.24 (<0.0001)	0.03 (0.3561)	0.07 (0.0208)	0.03 (0.2744)	0.06 (0.0581)	0.11 (0.0005)
Executive function (tolerate any delay)				0.30 (<0.0001)	0.24 (<0.0001)	0.02 (0.4262)	0.07 (0.0208)	0.06 (0.0594)	0.04 (0.1458)	0.10 (0.0009)
Memory (target actions)					0.84 (<0.0001)	0.02 (0.6342)	0.08 (0.0202)	0.08 (0.0143)	0.06 (0.0735)	0.28 (<0.0001)
Memory (ordered recall)						0.01 (0.8281)	0.11 (0.0008)	0.08 (0.021)	0.01 (0.7205)	0.26 (<0.0001)
Dietary diversity score							-0.01 (0.7389)	-0.01 (0.687)	0.05 (0.0972)	0.04 (0.2466)
Hemoglobin concentration								0.07 (0.0287)	0.06 (0.0364)	0.10 (0.0007)
Length-for-age z-score									0.14 (<0.0001)	0.26 (<0.0001)

Stimulation score	0.16 (<0.0001)

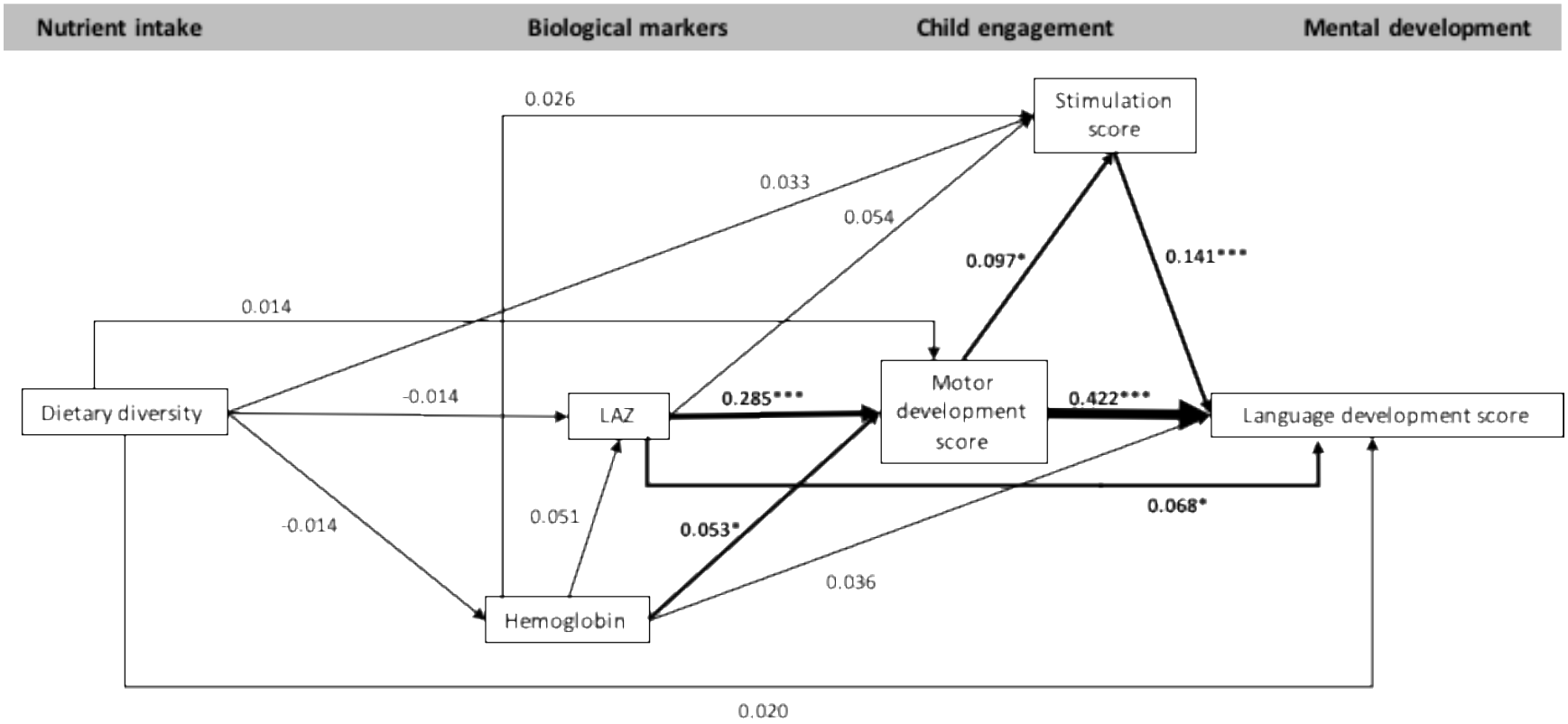
[1]Values are Pearson or Spearman rank correlation coefficients (p-value).

Figure 6.1: Hypothesized biopsychosocial model[1]



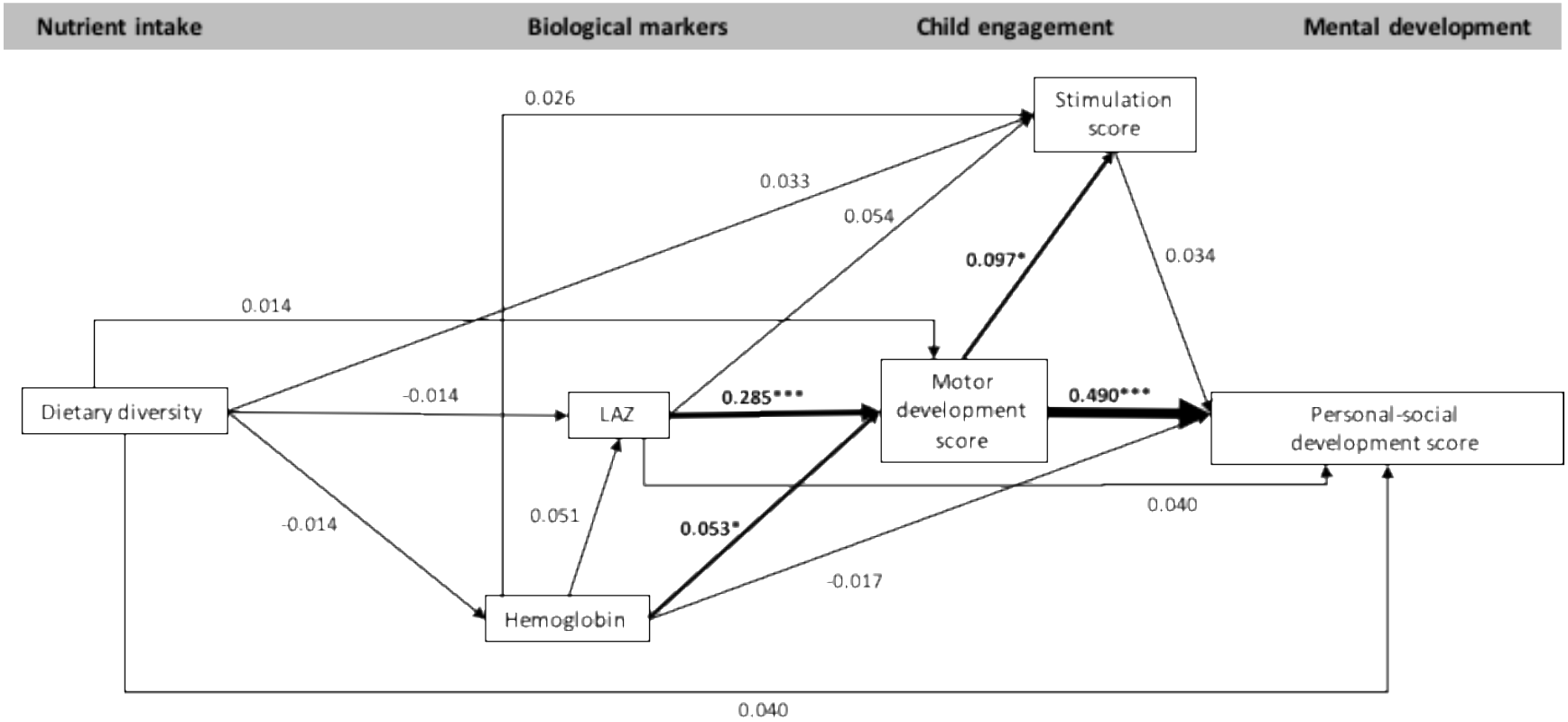
[1]All outcomes included in a single model for possible comparison. Length-for-age z-score (LAZ).

Figure 6.2: Standardized coefficients in path model between diet and language development of children 12-18 months of age (N=1079)[1]



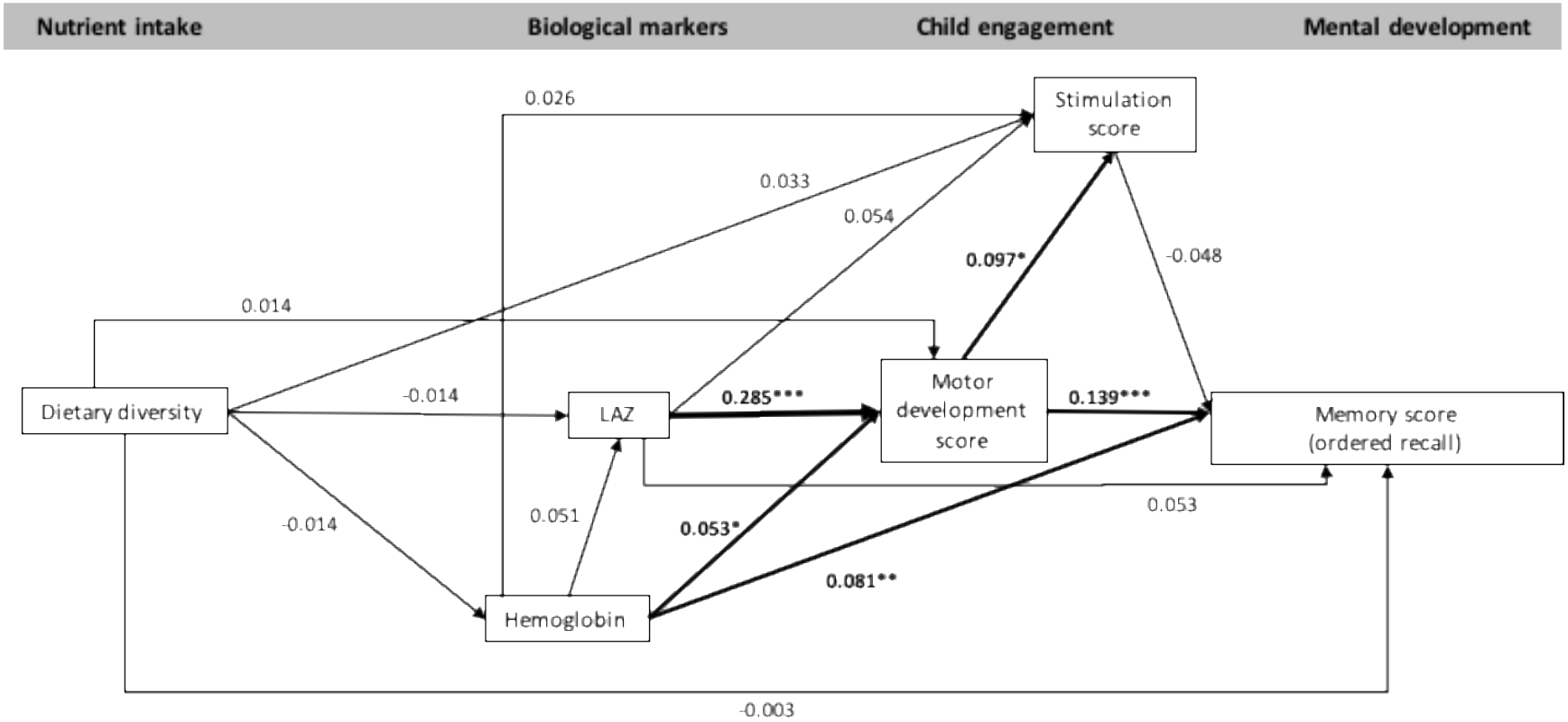
[1]Analysis adjusted for age of child, intervention group, wealth quintile, maternal education, child sex, religion, and caste, and accounted for clustering at the health sub-center level. * P<0.05; ** P<0.01; *** P<0.001. Analysis used Weighted Least Square Means with Missing Values. Length-for-age z-score (LAZ).

Figure 6.3: Standardized coefficients in path model between diet and personal-social development of children 12-18 months of age (N=1079)[1]



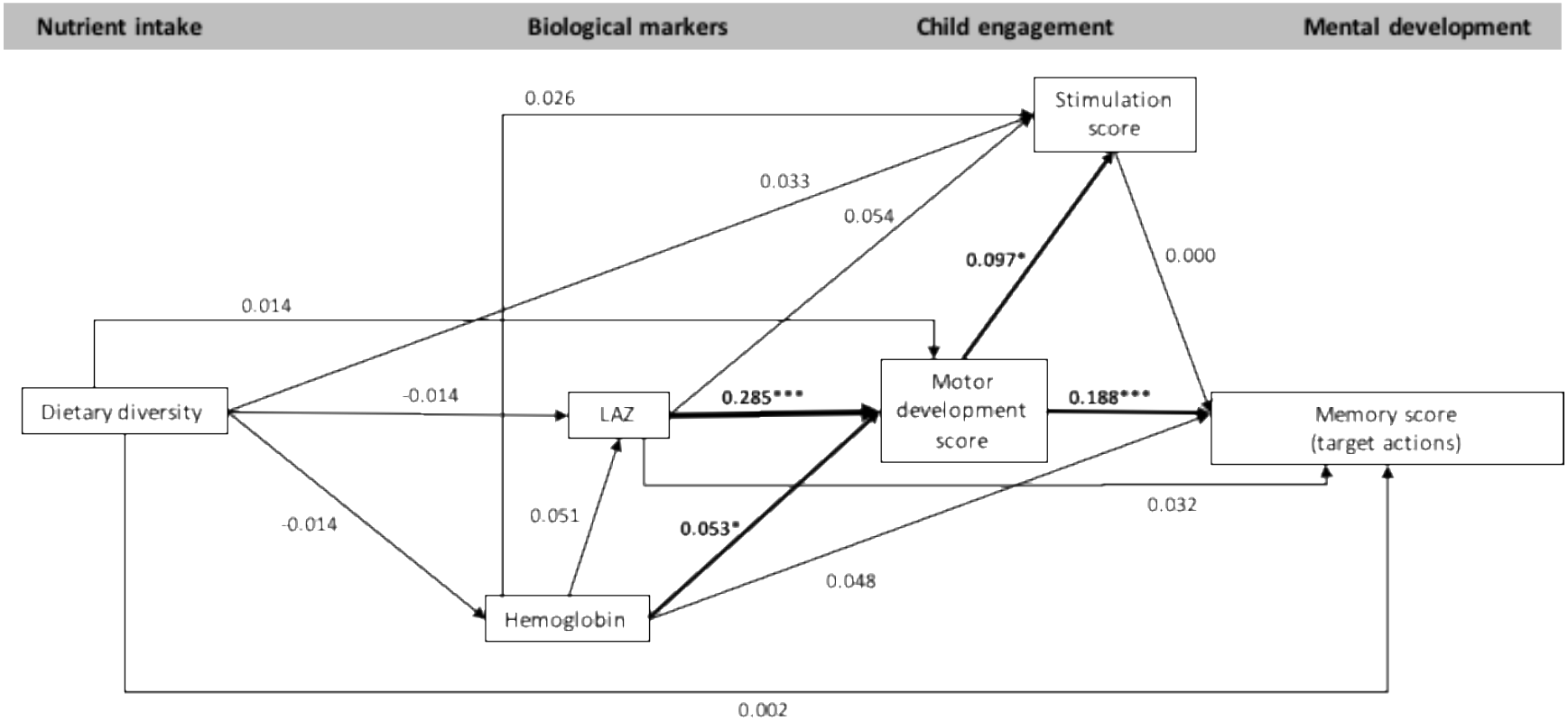
[1]Analysis adjusted for age of child, intervention group, wealth quintile, maternal education, child sex, religion, and caste, and accounted for clustering at the health sub-center level. * P<0.05; ** P<0.01; *** P<0.001. Analysis used Weighted Least Square Means with Missing Values. Length-for-age z-score (LAZ).

Figure 6.4: Standardized coefficients in path model between diet and memory score (ordered recall) of children 12-18 months of age (N=1079)[1]



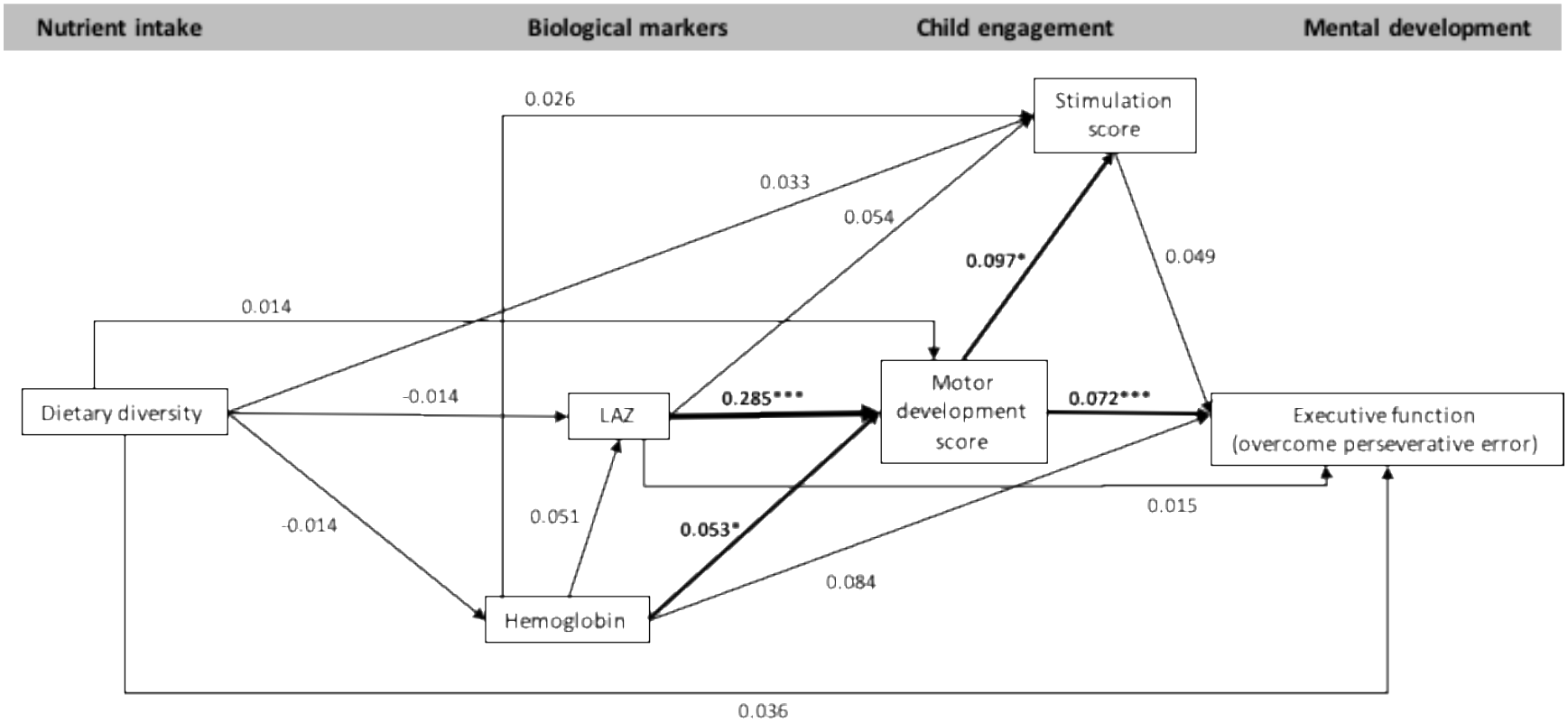
[1]Analysis adjusted for age of child, intervention group, wealth quintile, maternal education, child sex, religion, and caste, and accounted for clustering at the health sub-center level. * P<0.05; ** P<0.01; *** P<0.001. Analysis used Weighted Least Square Means with Missing Values. Length-for-age z-score (LAZ).

Figure 6.5: Standardized coefficients in path model between diet and memory score (target actions) of children 12-18 months of age (N=1079)[1]



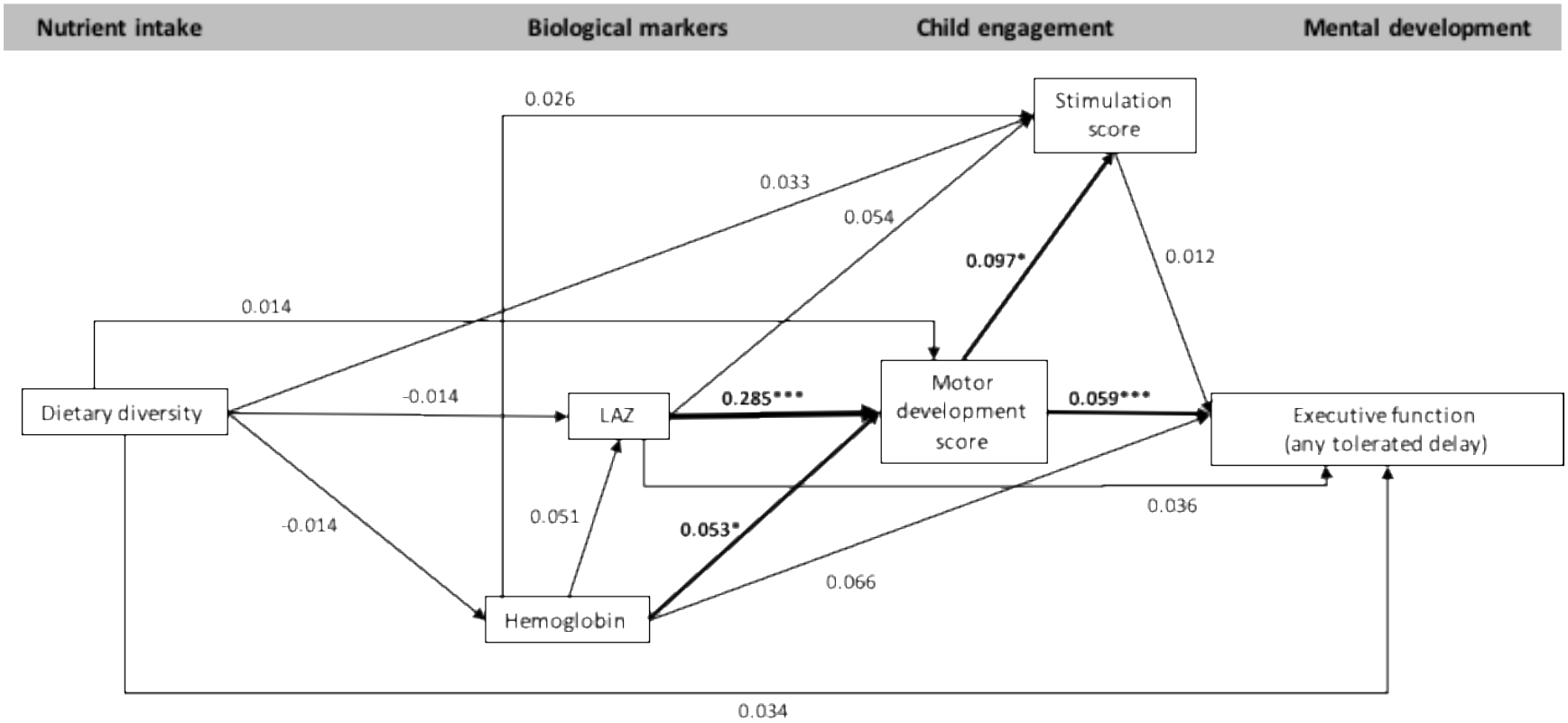
[1]Analysis adjusted for age of child, intervention group, wealth quintile, maternal education, child sex, religion, and caste, and accounted for clustering at the health sub-center level. * P<0.05; ** P<0.01; *** P<0.001. Analysis used Weighted Least Square Means with Missing Values. Length-for-age z-score (LAZ).

Figure 6.6: Standardized coefficients in path model between diet and executive function (overcome perseverative error) of children 12-18 months of age (N=1079)[1]



[1]Analysis adjusted for age of child, intervention group, wealth quintile, maternal education, child sex, religion, and caste, and accounted for clustering at the health sub-center level. * P<0.05; ** P<0.01; *** P<0.001. Analysis used Weighted Least Square Means with Missing Values. Length-for-age z-score (LAZ).

Figure 6.7: Standardized coefficients in path model between diet and executive function (any tolerated delay) of children 12-18 months of age (N=1079)[1]



[1]Analysis adjusted for age of child, intervention group, wealth quintile, maternal education, child sex, religion, and caste, and accounted for clustering at the health sub-center level. * P<0.05; ** P<0.01; *** P<0.001. Analysis used Weighted Least Square Means with Missing Values. Length-for-age z-score (LAZ).

Supplemental Table 6.1: R^2 values for path model

Dependent variable	**R^2**
Dietary diversity	0.011
Hemoglobin concentration	0.037
Length-for-age z-score	0.081
Motor development score	0.312
Stimulation score	0.100
Language development score	0.373
Personal-social development score	0.360
Memory score (pairs of actions)	0.122
Memory score (number of actions)	0.111
Executive function score (tolerated delay)	0.050
Perseverative error	0.060

Supplemental Table 6.2: Standardized direct, indirect, and total effects for path model[1]

		Standardized Coefficient (95% CI)		
Dependent variables	**Predictors**	**Direct Effect**	**Indirect effect**	**Total effect**
Hemoglobin concentration	Dietary diversity	-0.014 (0.052, 0.024)		
Length-for-age z-score	Dietary diversity	-0.014 (-0.071, 0.042)	-0.001 (-0.003, 0.001)	-0.015 (-0.071, 0.041)
	Hemoglobin concentration	0.051 (-0.002, 0.105)		
Motor development score	Dietary diversity	0.014 (-0.022, 0.050)	-0.005(-0.021, 0.011)	0.009 (-0.033, 0.050)
	Hemoglobin concentration	0.053 (0.010, 0.097)*	0.015 (0.000, 0.029)	0.068 (0.018, 0.118)*
	Length-for-age z-score	0.285 (0.238, 0.332)***		
Stimulation score	Dietary diversity	0.048 (-0.024, 0.121)	0.000 (-0.007, 0.006)	0.033 (-0.019, 0.085)
	Hemoglobin concentration	0.026 (-0.028, 0.080)	0.009 (0.003, 0.016)*	0.036 (-0.019, 0.090))
	Length-for-age z-score	0.054 (-0.021, 0.130)	0.028 (0.007, 0.048)*	0.082 (0.007, 0.156)
	Motor development score	0.097 (0.025, 0.169)*		
Language development score	Dietary diversity	0.020 (-0.019, 0.060)	0.007 (-0.016, 0.030)	0.027 (-0.020, 0.074)
	Hemoglobin concentration	0.036 (-0.009, 0.081)	0.037 (0.012, 0.063)*	0.074 (0.016, 0.131)*
	Length-for-age z-score	0.068 (0.021, 0.115)*	0.132 (0.098, 0.166)***	0.200 (0.134, 0.265)***
	Motor development score	0.422 (0.368, 0.475)***	0.014 (0.002, 0.025)	0.435 (0.379, 0.491)***
Personal-social development score	Dietary diversity	0.040 (0.007, 0.074)	0.005 (-0.017, 0.027)	0.045 (0.007, 0.084)
	Hemoglobin concentration	-0.017 (-0.061, 0.026)	0.037 (0.011, 0.062)*	0.019 (-0.032, 0.071)
	Length-for-age z-score	0.040 (-0.012, 0.092)	0.143 (0.115, 0.170)***	0.183 (0.123, 0.242)***
	Motor development score	0.490 (0.449, 0.531)***	0.003 (-0.002, 0.009)	0.493 (0.452, 0.534)***

Memory score (ordered recall)	Dietary diversity	-0.003 (-0.064, 0.058)	-0.002 (-0.010, 0.006)	-0.006 (-0.068, 0.057)
	Hemoglobin concentration	0.081 (0.037, 0.125)**	0.010 (0.001, 0.020)	0.091 (0.046, 0.137)**
	Length-for-age z-score	0.053 (-0.005, 0.112)	0.036 (0.017, 0.055)**	0.089 (0.030, 0.148)*
	Motor development score	0.139 (0.081, 0.197)***	-0.005 (-0.012, 0.002)	0.134 (0.075, 0.193)***
Memory score (target actions)	Dietary diversity	0.002 (-0.060, 0.064)	0.000 (-0.009, 0.010)	0.002 (-0.061, 0.066)
	Hemoglobin concentration	0.048 (-0.007, 0.104)	0.014 (0.003, 0.026)*	0.063 (0.006, 0.120)
	Length-for-age z-score	0.032 (-0.026, 0.090)	0.054 (0.033, 0.074)***	0.086 (0.026, 0.146)*
	Motor development score	0.188 (0.131, 0.245)***	0	0.188 (0.130, 0.246)***
Executive function (Overcome perseverative error)	Dietary diversity	0.036 (-0.033, 0.104)	0.001 (-0.005, 0.007)	0.036 (-0.034, 0.106)
	Hemoglobin concentration	0.084 (0.000, 0.156)	0.007 (0.000, 0.015)	0.092 (0.023, 0.161)*
	Length-for-age z-score	0.015 (-0.064, 0.095)	0.025 (-0.001, 0.050)	0.040 (-0.047, 0.127)
	Motor development score	0.015 (-0.064, 0.095)	0.005 (-0.004, 0.013)	0.077 (-0.003, 0.157)
Executive function (Any tolerated delay)	Dietary diversity	0.034 (-0.040, 0.107)	-0.001 (-0.006, 0.004)	0.033 (-0.042, 0.108)
	Hemoglobin concentration	0.066 (-0.005, 0.136)	0.006 (0.000, 0.013)	0.072 (0.002, 0.142)
	Length-for-age z-score	0.036 (-0.036, 0.109)	0.018 (-0.004, 0.040)	0.054 (-0.018, 0.127)
	Motor development score	0.059 (-0.015, 0.133)	0.001 (-0.006, 0.008)	0.060 (-0.013, 0.134)

[1]Values are β coefficients (95% CI). All adjusted for clustering at the health sub-center level. Adjusted analyses accounting for age of child in months, child sex, intervention group, wealth quintile of the household, religion, caste, and maternal education. Estimates of zero are not shown.

Supplemental Table 6.3: Unstandardized direct, indirect, and total effects for path model[1]

		Unstandardized Coefficient (95% CI)		
Dependent variables	**Predictors**	**Direct Effect**	**Indirect effect**	**Total effect**
Hemoglobin concentration	Dietary diversity	-0.016 (0.061, 0.028)		
Length-for-age z-score	Dietary diversity	-0.014 (-0.069, 0.041)	-0.001 (-0.003, 0.001)	-0.014 (-0.069, 0.040)
	Hemoglobin concentration	0.043 (-0.002, 0.088)		
Motor development score	Dietary diversity	0.050 (-0.081, 0.181)	-0.018 (0.078, 0.042)	0.032 (-0.120, 0183)
	Hemoglobin concentration	0.167 (0.029, 0.305)*	0.046 (0.001, 0.091)	0.213 (0.055, 0.371)*
	Length-for-age z-score	1.070 (0.874, 1.266)***		
Stimulation score	Dietary diversity	0.048 (-0.024, 0.121)	0.000 (-0.010, 0.009)	0.048 (-0.027, 0.123)
	Hemoglobin concentration	0.033 (-0.034, 0.099)	0.012 (0.004, 0.019)*	0.044 (-0.023, 0.112))
	Length-for-age z-score	0.081 (-0.033, 0.195)	0.041 (0.010, 0.072)*	0.122 (0.009, 0.235)
	Motor development score	0.038 (0.009, 0.067)*		
Language development score	Dietary diversity	0.038 (-0.036, 0.112)	0.013 (-0.030, 0.055)	0.051 (-0.038, 0.139)
	Hemoglobin concentration	0.058 (-0.015, 0.131)	0.059 (0.018, 0.101)*	0.118 (0.024, 0.211)*
	Length-for-age z-score	0.130 (0.041, 0.219)*	0.252 (0.186, 0.317)***	0.381 (0.256, 0.507)***
	Motor development score	0.215 (0.187, 0.243)***	0.007 (0.001, 0.013)	0.222 (0.192, 0.251)***
Personal-social development score	Dietary diversity	0.097 (0.015, 0.179)	0.012 (-0.041, 0.065)	0.109 (0.016, 0.202)

	Hemoglobin concentration	-0.036 (-0.125, 0.054)	0.075 (0.021, 0.129)*	0.040 (-0.067, 0.146)
	Length-for-age z-score	0.099 (-0.028, 0.226)	0.350 (0.280, 0.420)***	0.449 (0.303, 0.596)***
	Motor development score	0.321 (0.293, 0.349)***	0.002 (-0.001, 0.006)	0.323 (0.296, 0.351)***
Memory score (ordered recall)				
	Dietary diversity	-0.003 (-0.066, 0.059)	-0.002 (-0.011, 0.006)	-0.006 (-0.070, 0.059)
	Hemoglobin concentration	0.071 (0.032, 0.110)**	0.009 (0.001, 0.017)	0.080 (0.040, 0.120)**
	Length-for-age z-score	0.056 (-0.006, 0.118)	0.037 (0.018, 0.057)**	0.093 (0.031, 0.156)*
	Motor development score	0.039 (0.023, 0.055)***	-0.001 (-0.003, 0.001)	0.038 (0.021, 0.054)***
Memory score (target actions)				
	Dietary diversity	0.003 (-0.097, 0.103)	0.001 (-0.014, 0.016)	0.004 (-0.099, 0.107)
	Hemoglobin concentration	0.067 (-0.009, 0.144)	0.020 (0.004, 0.036)*	0.087 (0.007, 0.168)
	Length-for-age z-score	0.054 (-0.043, 0.150)	0.089 (0.054, 0.124)***	0.143 (0.042, 0.243)*
	Motor development score	0.083 (0.058, 0.109)***	0	0.083 (0.058, 0.109)***
Executive function (Overcome perseverative error)				
	Dietary diversity	0.031 (-0.029, 0.092)	0.001 (-0.004, 0.006)	0.032 (-0.030, 0.093)
	Hemoglobin concentration	0.064 (0.000, 0.117)	0.006 (0.000, 0.011)	0.069 (0.017, 0.121)*
	Length-for-age z-score	0.014 (-0.057, 0.085)	0.022 (-0.001, 0.045)	0.036 (-0.042, 0.114)
	Motor development score	0.017 (-0.002, 0.036)	0.001 (-0.001, 0.003)	0.018 (-0.001, 0.038)
Executive function (Any tolerated delay)				
	Dietary diversity	0.029 (-0.037, 0.095)	0	0.029 (-0.037, 0.095)

Hemoglobin concentration	0.050 (-0.003, 0.102)	0.005 (0.000, 0.010)	0.054 (0.002, 0.107)
Length-for-age z-score	0.033 (-0.032, 0.098)	0.016 (-0.004, 0.036)	0.049 (-0.017, 0.114)
Motor development score	0.014 (-0.003, 0.032)	0	0.015 (-0.003, 0.032)

[1]Values are β coefficients (95% CI). All adjusted for clustering at the health sub-center level. Adjusted analyses accounting for age of child in months, child sex, intervention group, wealth quintile of the household, religion, caste, and maternal education. Estimates of zero are not shown.

Chapter 7: Discussion

The main findings from the four aims of this dissertation are as follows:

1. A meta-analysis of 33 studies indicated that prenatal nutrition interventions did not have a significant effect on mental development of offspring before the age of two years, whereas postnatal supplementation of children under two years of age consisting of macronutrients, multiple micronutrients, and single micronutrients had a significant effect on mental development in low- and middle-income countries.
2. Using cross-sectional data from a baseline survey, dietary diversity, length-for-age z-scores (LAZ), and stimulation were significantly associated with motor and mental development of children 6-18 months of age living in Bihar, India. The association between dietary diversity and mental development was mediated by gross motor skills, fine motor skills, and stimulation.
3. An effectiveness trial of home fortification with multiple micronutrient powders (MNPs) showed a significant impact on motor and mental development of children 6-18 months of age in Bihar, India. Greater impacts of MNPs on motor and mental development were observed in children from households with higher stimulation scores at baseline compared to those from households with lower stimulation scores at baseline.
4. Using cross-sectional data from an endline survey, a path analysis in children 6-18 months of age in Bihar demonstrated strong and consistent associations between LAZ and motor development, and between motor development and language, personal-social, memory, and executive function abilities. Further, stimulation had a significant association with language development, as did hemoglobin with memory.

Findings from the dissertation add to the evidence for the effects of multiple micronutrients on motor and mental development in young children from at-risk populations. In particular, it adds to the limited research on effectiveness of nutrition interventions in settings where overworked frontline health workers are the delivery agents. The overall literature on nutrition and child development in resource-poor settings shows mixed outcomes. There is more evidence of impact of postnatal supplementation (starting at six months of age) than for prenatal supplementation. There is also consensus on giving priority to populations suffering from malnutrition to achieve an impact on child development. Our findings support this conclusion with significant, yet modest, effects on child development from multiple micronutrient supplementation. Effect sizes were small ($d<0.20$) but similar to those found in multiple micronutrient effectiveness trials in malnourished populations of the same age range (1). The intervention also resulted in a modest yet significant decrease in the prevalence of anemia and diarrhea, as described elsewhere (2). Further, we demonstrate the importance of investigating various cognitive functions, so as to highlight effects on specific functions and skills at select ages rather than a global measure of development. Our findings also emphasize the role that nutrition can play on child development, directly and indirectly through associations with growth, motor skills, hemoglobin, and stimulation. In accordance with previous studies, direct associations were observed between dietary diversity, LAZ, stimulation and motor and mental development. We also found that the association between dietary diversity and mental development was mediated by stimulation because mothers who offer diverse diets also tend to provide more stimulation to their child. Stimulation, in turn, is strongly associated with mental development. Few studies have examined and demonstrated such mediation. In a path analysis, which was able to examine how our data fit the model of a theoretical framework, we observed strong direct and indirect relations between LAZ, motor development and cognitive abilities. Stimulation and hemoglobin also saw associations with language and memory skills, respectively. Few such path models using biological measurements of

hemoglobin, and a combination of parent-report and behavioral child development measures have been examined in a young malnourished population. The relationships observed clarify how important these mediators are and how interventions to target them may work in synergy to augment desired effects.

7.1 Generalizability of findings from the Bihar trial

Child development findings from the Bihar trial are likely to generalize to settings with similarly high rates of malnutrition, in populations with a similar potential to benefit from MNPs, where effects modifiers of the impact of MNPs on child development are comparable (i.e. household stimulation), and where frontline health worker visits are part of the routine health infrastructure. According to the National Family Health Survey (NFHS) -4, 48% of children under five years of age are stunted and 64% are anemic in Bihar (3). These rates are high and present an overall state of health that could benefit from MNPs. Similar effects may not be seen in populations with lower rates of malnutrition and especially less anemia. For instance, in an effectiveness trial in Newfoundland, Canada, iron supplementation from 1-6 months of age in a sample of infants with no anemia and mean baseline hemoglobin concentration of 12.5 g/dL found no improvements in mental development as measured with the Bayley Scales of Infant Development (BSID) (4). In another effectiveness trial in children 12-24 months living in marginal rural communities in Mexico, MNPs compared to a placebo did not improve mental or motor development as measured with the BSID-II. Baseline status of the children was better than that seen in Bihar: the sampled population had a baseline hemoglobin concentration of 11.9 g/dL and prevalence of stunting was 19% (5).

Likewise, similar effects may not be seen in populations with better levels of characteristics that were found to be effect modifiers. Evidence from our baseline survey suggests a relatively low level of psychosocial stimulation provided in the home and significant effect modification from the level of

stimulation. Importantly, children in our sample aged 6-18 months were not eligible to attend preschool centers (typically for children 3-6 years of age); therefore, most of the stimulation to which children were exposed came from activities and materials in the home. Our study used the Family Care Indicators (FCIs) to examine level of stimulation in the home with questions about availability of play materials and books, time spent outside the home, singing, telling stories, counting and naming objects with the child. In our survey, responses on the FCI indicated that 77% of children played with store-bought toys, 49% played with homemade toys, 15% of children had family members tell stories to them, and 10% had family members read or look at picture books with them. These rates are low compared to resource-rich settings (6); however, scores are fairly typical when compared to rural parts of other low- and middle-income countries (LMICs), such as Bangladesh. In a study of children 18 months of age in rural Bangladesh, similar levels of stimulation were found, where 85% played with store-bought toys, 48% played with homemade toys, 30% were read to or were shown picture books, and 17% were told stories (7). Analyzing data from the Multiple Indicator Cluster Survey-3 which uses six questions from the FCI, Bornstein et al. reported caregiving practices of infants 0-12 months in 38 LMICs. Wide variation in practices was seen and prevalence tended to be higher in high Human Development Index (HDI) countries and lower in low HDI countries. For example, no caregivers read to their children in Burkina Faso whereas 54% did in Trinidad and Tobago. Further, only 3% of caregivers told stories to their children in Laos, whereas 61% performed this activity in Trinidad and Tobago (6). As seen in our impact analysis of the Bihar trial, the baseline level of stimulation may modify the effect of a nutrition intervention on child development, wherein children from households with higher levels of psychosocial stimulation would benefit more from nutrition than children with lower levels. Our study was not able to establish an exact psychosocial stimulation level at which nutrition may be more effective in improving development. This is an area of research that needs

exploring and would be useful for public health messaging, and also for the importance of local early care centers and their use as a potential platform for nutrition interventions and programs.

Many other countries use frontline health workers (FLWs) to deliver health messaging and products to women, men, and children in even the remotest parts of the country. The success of a program such as the one demonstrated in Bihar depends largely on the FLW's coverage and frequency of visits, as well as compliance of the household members who receive the product. As a first level, the FLW must reach the household to provide the supply of MNPs, but they must also convince the caregiver to give the MNP to the child. The results of the Bihar study were particularly meaningful because it was conducted in a setting with overworked FLWs who had no additional incentive to deliver the MNPs other than for the perceived good of the children. In an effectiveness trial in Pakistan with low coverage of MNPs (between 14-19% of households received a 60-day dose) and compliance (11% of those who received the dose did not give it to their child, mostly based on the belief that the powder would make their child sick), a significant impact was still observed on language development of children (1). Consequently, our findings are likely to generalize to places where the health system's use of FLWs is similar.

7.2 Home fortification with multiple micronutrients in the context of other food fortification strategies

Home fortification with MNPs involves behavioral change on the part of the mother, who is required to mix the package contents into her child's food. This small act can result in children receiving up to 25 different micronutrients (8) in a single meal. The message is simple and the potential to benefit the child's micronutrient status is large. Yet effectiveness trials to date show poor compliance. The combination of poor compliance and poor coverage suggests low sustainability of

certain MNP programs, such as ours, if improvements are not made prior to scaling up. As mentioned previously, there is evidence for factors that can enhance coverage and compliance, but within systems where FLWs are already overworked, it is worth considering alternatives. How does the MNP program compare with other fortification programs and interventions?

The premise for food (compared to home) fortification is that 1) rather than changing individuals' diets or requiring regular consumption of supplements, the consumption of fortified foods does not require behavior change, so uptake will be high; and 2) due to the regular consumption of fortified foods, levels of fortification do not need to be as high as those of supplements to achieve the same outcomes on health, at least in adults. Two important examples of the potential for food fortification are the achievements seen from folic acid fortification of flour and iodine fortification of salt. Through fortification of flour with folic acid, consumption of folic acid increased in preconception women and this has contributed to an enormous reduction in birth defects (9, 10). Salt iodization and other iodine fortification strategies have increased urinary iodine levels of populations and reduced the prevalence of goiter, miscarriage, stillbirth, and infant death (11-17). Other products being fortified currently include oil, sugar, rice, bouillon cubes, maize flour, and sauces.

Unlike home fortification with MNPs, food fortification does not involve behavior change, but is highly dependent on effective marketing of the fortified product. If products are not properly marketed, they may not reach their targeted audience, and even if they reach the audience they may not be consumed. For instance, a double fortified salt (DFS) effectiveness trial in Bihar showed that, when DFS was sold through the market, 42% of households ever tried it (but only 14% were using it at the time of the endline survey) (18). However, in villages where an edutainment movie was screened and in villages where shopkeepers were provided an incentive to sell DFS, uptake was 5 percentage points higher. Even when DFS was delivered for free to households, as a separate experiment, only 61% of households were using the salt (18). When governments are involved, fortified products may reach

more households if the government makes them the only option available through subsidized programs. For example, in India, the use of government-subsidized ration shops as the avenue for distribution allows fortified foods to reach a large majority of the population, particularly the poor, in remote parts of the country. This is already happening in some states with the distribution of DFS.

Food fortification is a sustainable option to reach millions, but limitations remain with respect to cost and organoleptic changes of certain fortified foods. The upfront costs of equipment necessary to produce certain fortified foods may be high. For instance, the cost of the equipment necessary for making the encapsulated ferrous fumarate (EFF) DFS premix is US$ 600,000-1,000,000. The equipment for blending EFF DFS is US$ 15,000-25,000 (19). However, the investment into these costs may be worthwhile if it reduces production costs overall and if the product is more acceptable than a cheaper option that consumers do not buy. In other cases, stability and sensory issues have been reported as a limitation in adoption. For instance, DFS using ferrous sulphate has been show to turn a yellow-brown color in high humidity (20). In other cases, cooking can cause color changes and extended boiling can result in the formation of a yellowish layer on the top of the water (21). Despite the strides made in the technology to date, there still remain important issues with certain fortified foods before scaling up.

Food fortification still has its limits with respect to reaching all populations in need with adequate amounts of nutrients. In a context such as rural Bihar, many commercially available products such as ready-to-eat cereals, milk, sugar, or butter, which are those currently easiest to fortify, are too expensive for the majority of households. For instance, most villages in India use chakki mills, or local village-level mills, to process their flour. The large number of chakki mills in each district and limitations with maintaining quality makes fortification of wheat flour challenging in this context. Further, typically fortified foods are fortified at levels that will keep nutrient intakes below the tolerable upper level for men, the group with the greatest consumption of staples. Because children

generally eat less than men, they often do not consume enough to bridge the gap in nutritional requirements. Inadequate fortification levels for children can be addressed by designing foods specifically for them, such as fortified complementary foods, and using nutrient concentrations that meet their needs. These are however expensive.

Some evidence exists for the impact of food fortification programs on micronutrient status, yet most use cross-sectional designs, which often limits their ability to attribute benefits to the program. However, some cross-sectional analyses have been able to document a plausible impact pathway. For instance, an analysis of cross-sectional data before and after a food fortification program in Costa Rica showed improvements in anemia and hemoglobin (22). Some confidence was established in the impact of fortification because the authors were able to determine a likely pathway through dietary intake measurements and refute plausible pathways besides food fortification, such as decreased infection, poverty, or sanitation. Further, limited evidence exists for effects on functional outcomes beyond neural tube defects and goiter. Few randomized controlled trials have examined impacts on child development, for instance. One example is an effectiveness trial in Ethiopia which examined the impact of salt iodization on mental development of infants and young children and found significant improvements in cognitive, receptive language, and fine motor development compared to children from communities in which iodized salt was available 4-6 months later (23). Another effectiveness trial in India examined the effect of using DFS compared to iodized salt to prepare school meals (24). They found improvements from DFS on reading and math scores, particularly among children from non-disadvantaged backgrounds. Neufeld and Friesen called for more evidence on the impact of food fortification programs using appropriate designs, in deficient populations using suitable fortified foods, and effective monitoring strategies guided by thoughtful program impact pathways (25).

7.3 The small effects of nutrition interventions on child development

Large follow-up studies and more recent, well-powered, studies suggest a significant benefit of early improved nutrition on development (1, 26-30). However, as summarized by Larson and Yousafzai, effects of nutrition interventions in children under two years of age are significant yet small (Cohen's d effect size 0.08, 95% CI 0.02, 0.13) (31). Several reasons exist for why effects of nutrition interventions may not be as large as previously anticipated or, for instance, as large as those seen from stimulation interventions. For one, many pathways exist between nutrition and its effects on child development, and some of these pathways are not often measured or their measurement is inconsistent across studies. Second, the majority of nutrition interventions take place in at-risk populations, who despite having the potential to benefit from enhanced nutrition, may also have other constraints that minimize the benefit. For example, they may have infections and macronutrient deficiencies that are not addressed by micronutrient interventions. Both explanations will now be discussed in greater detail.

As described in the path analysis paper examining the various pathways between dietary diversity and child development, morbidity is an important mediating variable on the pathway between nutrition and development. However, frequency and severity of episodes of diarrhea, fever, cough, or vomiting are difficult to assess. Many public health surveys resort to measuring parent-reported presence of morbidity in the prior week or two. Although this may give a rough approximation for monitoring morbidity, the level of detail and short time frame is not enough to accurately examine the role of improved nutrition on child development through reduced morbidity. Tracking long-term illness and morbidity, however, requires repeated home visits, consistent personnel, and funds. Further, in intervention trials, researchers must perform the same amount of monitoring and home visits in both intervention and control groups because visits themselves can influence the outcome of child development by bringing parental attention to the child's health and wellbeing. Along the same lines as morbidity, infection is an important variable on the pathway between nutrition and development.

Infection can be measured in various ways, through surveys on water access and use, sanitation practices, and hygienic appearances. Infection can also be measured with blood biomarkers such as C-reactive protein or alpha1-acid glycoprotein.

Another blood biomarker of importance is hemoglobin. As demonstrated in the path analysis paper, hemoglobin can be an important mediator between nutrition and certain cognitive functions, such as memory, but may be less important for other cognitive domains, such as executive function and language and personal-social development. As such, the effects of nutrition interventions may be partially dependent on their effects on hemoglobin. In Larson et al.'s systematic review and meta-analysis of the association between hemoglobin and child growth and development, the change in hemoglobin resulting from iron interventions in children under five years of age was associated with change in growth and mental development scores (32). Therefore, measuring a mediating indicator such as hemoglobin concentration may clarify the responses observed, or lack thereof, on child development.

In many resource-poor settings, micronutrient and macronutrient deficiencies still persist. The micronutrient elements provided in many recent trials still may not target the majority of deficiencies in a population. This may explain the observed small or non-significant effects on child development. This also applies to multiple micronutrient trials. In food insecure areas, energy levels may be low because children have a low caloric intake. In this case micronutrients may not be enough to see improvements on motor or cognitive functioning. Interventions that provide macronutrients may still lack the necessary quality even if quantity is sufficient. This is an area still under investigation in the human literature, whereas in animal studies, the ideal fatty acid pattern and amino acid pattern for proteins is well understood (33). Ultimately, an unaddressed deficiency may be the major limiting factor for an impact on child development. The same idea applies to psychosocial stimulation. As evidenced in the Bihar impact study on child development, improvements on motor and mental

development were larger in children with higher levels of baseline stimulation. So the effect of limited additions of nutrients may remain small if home stimulation is low, as it is in most LMICs. Future research needs to examine the specific level of stimulation at which effects of nutrition are stronger. The message that a proper foundation is needed to benefit more from such an intervention has been replicated in other studies in addition to ours (34, 35). Ultimately, the lack of basic nutrition and stimulation resulting from food insecurity and poverty may contribute to the small effects observed on child development from nutrition interventions.

7.4 What evidence means for decision making

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was developed as an approach to link quality evidence to recommendations. GRADE uses a systematic approach to rate the quality of studies based on study design limitations, inconsistency of results between studies, indirectness of evidence, imprecision, and reporting bias (36). Using these criteria, the majority of recommendations are based on systematic reviews of randomized controlled trials (RCTs) only.

Systematic reviews of the effects of nutrition interventions on child development have not been conclusive enough to develop a recommendation. Furthermore, they have repeatedly shown smaller effects than psychosocial stimulation interventions. A meta-analysis of nutrition and stimulation interventions in children under two years of age in resource poor settings described a larger effect from stimulation (Cohen's d effect size = 0.42, 95% CI 0.36, 0.48 for cognitive development and d = 0.47, 95% CI 0.37, 0.56 for language development) compared to nutrition interventions (d=0.09, 95% CI 0.036, 0.14 for mental development) (37). Nutrition and psychosocial stimulation are often combined in interventions but only rarely in a factorial design. Evidence suggests that interventions combining

nutrition and stimulation show no detriment to child development compared to the provision of either intervention alone, yet there do not seem to be any synergistic effects (38). However, in the short term, some studies in undernourished populations have shown an additive effect (26, 39). More evidence is needed to examine reasons for the differences in findings.

Psychosocial stimulation interventions may demonstrate larger effects on development, but nutrition interventions also offer advantages. First, the cost of nutrition interventions is relatively small compared to psychosocial stimulation interventions. Stimulation programs involve more in-depth training of workers and supervisors, including in-service training, and stimulation materials. A study in rural Pakistan that used existing FLWs estimated that the cost of a responsive stimulation intervention integrated in an existing community-based health and nutrition service is approximately US$ 4 per month per child (40). Comparatively, nutrition supplementation is cheaper. For example, weekly iron and folic acid (IFA) supplementation for women costs between US$ 0.15-0.36 per recipient per annum in India (41). Food fortification can also be relatively inexpensive; it is expected that adding the EFF DFS premix to iodized salt would increase the cost between US$ 0.047-0.067 per kg of iodized salt compared to regular iodized salt (19). Second, it would be a missed opportunity to offer only one type of intervention. Nutrition and stimulation interventions target several distinct and common pathways that can ultimately improve development. Further, nutrition and stimulation are both topics that appeal to parents; by combining both interventions, there may be additional interest and buy-in from parents. Nutrition and stimulation activities can be built into combined interventions, such as responsive feeding practices that incorporate story-telling, singing or rhyming with the child. In such an intervention, children may eat more while developing important skills with their caregiver. Lastly, nutrition is important because it can touch on many aspects of a child's life, such as nutritional status, immunity, physical activity, and cognitive development. In fact, nutrition has been placed at the heart of the Sustainable Development Goals, with potential to impact earning capacity, hunger, health,

learning potential, women's empowerment, to reduce inequality, and much more. It is estimated that every $1 invested in nutrition gives $16 in return (42).

When faced with the option to scale up home fortification with MNPs for the ultimate goal of improving child development, governments should examine their population's nutritional and stimulation status, gaps in current programs, and existing health infrastructure on which to build to inform their decision. Piloting such a program is essential to estimate the potential for impact, and identify any gaps or issues in the program impact pathway (e.g., supply chain, product delivery, messaging) prior to scaling up.

7.5 Implications for future research

The Bihar study adds to a small number of micronutrient effectiveness trials that generated mixed results in terms of effects on child development. While reflecting on the successes and limitations of ours and others' work, there are several key components that merit more discussion, including measurement tools, age of intervention, population's baseline status, type of nutrition delivered, and leveraging the existing health system and infrastructure.

7.5.1 Measurement of child development

Several criteria might be considered when selecting measures of child development for children under two or three years of age. Compendiums of measures such as the The Brain Development Measurement Tests Matrix and the Toolkit (43) describe a variety of measures with the aim of encouraging researchers to converge on ones that cover critical abilities (e.g. motor, cognitive, language, executive function, socio-emotional), that have been commonly used in LMICs, and can be

administered by non-professionals. They point out that even though norms may not be available in LMICs for such tests, their reliability and validity should be assessed in each context where used.

The majority of studies assessing children under three years of age in LMICs have used parent report tools, such as the Developmental Milestones Checklist (DMC) and the Ages and Stages Questionnaire, or direct child assessments, such as the BSID, the Griffiths Mental Development Scales, and more recently the Malawi Developmental Assessment Tool. Many nutrition studies rely on parent report, though these have their strengths and their limits. Most are relatively quick and can be performed by trained non-specialists, yet they are subject to respondent bias. Direct assessments of children, such as the executive function and memory tests we used, are particularly useful regarding skills that parents are unlikely to be able to report on. However, they also have limits. In our Bihar study, we found it difficult to establish reliability measures for our data collectors, particularly with the memory test, because children expectedly perform better on these tests when they complete them several times. Further, direct assessments are subject to the respondent's personality and mood (i.e., shyness or refusing to perform tasks). As in all research in LMICs, researchers find the need to modify their measures for the context, especially language tests, but this is commonly accepted as long as the level of difficulty and the underlying construct is maintained, and the test is validated. Concurrent validity is performed by examining the new test scores' sensitivity to child age, maternal education, nutritional status, level of stimulation, and other variables one would expect development to correlate with. In our case in Bihar, tests showed adequate concurrent validity. Convergent validity, such as demonstrating scores comparable to those obtained with a different test of the same construct such as the BSID is available for the DMC in an African country (44), but not in India. Another important criterion is that the ability being tested be considered important either for functioning at the current age of the child and/or for future progress. In Bihar, we used tests that assess two specific cognitive

functions (executive function and declarative memory) that have been shown to be predictive of later intelligence (45).

Direct brain measurements, such as electroencephalography (EEG), event-related potentials, and functional near-infrared spectroscopy are another way to assess mental development. They were not considered in our study because they require specialized expertise and equipment. Brain imaging studies can attribute outcomes from interventions to changes in striatal, hippocampal, and prefrontal cortex functioning and changes in neurotransmitter signaling pathways. Many do not require a behavioral response and thus create a unique opportunity to examine brain development non-invasively in a sensitive manner in infants as young as a few days old. For instance, recognition memory has been examined in neonates by recording electrical potentials on the scalp's surface in response to auditory stimuli of the child's mother's voice compared to a stranger's voices (46). Although these types of measurements can be challenging in remote settings, some initial work has been conducted in LMICs. For instance, Tarullo et al. recently conducted EEG measurements in a subsample of children included in an RCT (1) in rural Pakistan. They found that an increase in EEG power in gamma frequency bands was associated with better executive function and cognitive abilities at four years of age (47). Importantly though, authors note that more than half the data were excluded (114 children out of 219) largely due to technical difficulties and electrical noise because electricity was only available for half the day. The relevance of specific differences in brain recordings will need to be made explicit by researchers by linking certain sites and wave forms to specific mental functions. Still, we expect to see an increasing number of studies published using brain recording from children in LMICs in the coming years.

7.5.2 Age of intervention

The first 1000 days has been marked as a period of sensitivity - sensitivity to insult as well as positive events. These are the days of rapid changes in development, during which brain structures and functions are most vulnerable. For instance, if adversity is present during the period of dendritic arborization, the hippocampus and prefrontal cortex can sustain damage that compromises functional abilities (48). The same principle applies to positive supports through nutrition and other interventions during this period. For instance, Pollitt et al conducted a follow-up of a 3-month energy supplementation trial given to children 6-60 months of age (49). Eight years later, children who had received the supplement did not perform better than control group children on tests of information processing, vocabulary, word fluency, and arithmetic. Importantly, when the analysis was constrained to children who had received the supplement before 18 months of age results showed a significant effect of the intervention on working memory. Some level of brain recovery from a deficient state may depend on the timing of the intervention and the brain region's requirements for that nutrient at the time. Nutrition supplementation during the prenatal period has not shown conclusive evidence for effects on development (31) despite this being a time of rapid development. Mixed results could be due to the small number of studies, different timings of interventions and intervention types, and varying populations. In resource-limited settings, it is often difficult to identify and start interventions in women early in pregnancy when the initial stages of fetal growth and development occur. Further, women are often deficient in more than one micro- or macronutrient and supplementation targeting only one deficiency may not be enough to see effects on infant development. Preconception interventions may lead to larger effects because the fetus would be exposed to a better nutritional state throughout gestation, but few trials exist which report effects on early child development (50). Others have examined whether supplementation of mothers during pregnancy and children during infancy has larger effects on cognition than just one or the other intervention (29, 30, 51-53), but results are mixed

and too few comparable trials exist to make conclusive statements. Some evidence exists for still significant effects on cognition from interventions delivered after childhood, specifically for iron supplementation. A review of 14 RCTs of children above six years of age, adolescents, and adults found that iron supplementation improved attention (SMD 0.59; 95% CI: 0.29, 0.90), and among anemic populations, iron improved IQ by 2.5 points (95% CI: 1.2, 3.8) (54). These findings suggest that iron may be important for cognition throughout the life course. The evidence for effects from nutrition interventions other than iron beyond childhood has not been demonstrated.

7.5.3 Baseline status of the population

As described previously, the baseline deficiencies present in a population may dictate how responsive children will be to a certain nutrition intervention, wherein malnourished populations have a larger potential to benefit from nutrition interventions than well-nourished populations. For instance, Stolzfus et al found effects of iron supplementation on motor development only among children with low hemoglobin (<90 g/L) (55). Corroborating their finding, a recent review performed by Larson et al of iron supplementation trials on growth, motor, and mental development in children under five years of age found a trend for a negative association between baseline hemoglobin and effects on growth and development (i.e. larger effects of iron supplementation on growth and development among populations with lower initial hemoglobin concentration) (32). Psychosocial stimulation can also vary widely between different settings. Bornstein et al examined types of stimulation (such as singing, telling stories, naming and counting with the child) received by infants from 38 different countries and found that prevalence varied significantly among countries, even among low- and middle-income countries (6). For example, no caregivers read to their children in Burkina Faso whereas 54% did in Trinidad and Tobago. Or only 3% of caregivers told stories to their children in Laos, whereas 61%

performed this activity in Trinidad and Tobago. They also found that different stimulation domains are related to different cognitive domains. These findings suggest that it is important to accurately establish the baseline status of a population prior to administering a nutrition intervention to ensure potential to benefit and test the limits of benefit. Few RCTs examine effect modifiers such as baseline hemoglobin, LAZ, stimulation, and food security. The study of predetermined effect modifiers needs to be added to future nutrition RCTs, particularly in LMICs where these baseline conditions can vary from household to household.

7.5.4 Types of nutrients

Micronutrients have gained importance over the past decade, with many studies reporting effects on micronutrient status and growth. Yet, when looking at effects on child development, the effects of micronutrients are not as clear. Larson and Yousafzai's meta-analysis of nutrition interventions in children under two years of age indicated that the overall effect from energy, fats, and food supplementation on mental development was significant, whereas effects from single and multiple micronutrient supplementation were not (31). The evidence for combined macro- and micro-nutrient interventions is promising, with more recent studies being published using lipid supplementation in addition to micronutrients (28-30). Yet, in terms of effects for micronutrients alone, too few comparable well-powered, randomized trials in young children exist to make conclusions. Other studies, not included in the meta-analysis highlight the importance of animal source foods for development. Flesh foods in particular have readily available iron in the form of heme-iron and provide other essential nutrients, proteins, and energy. A trial in Kenyan school children found that the provision of meat improved muscle mass, much more so than milk or plant-based foods (56). Children supplemented with meat also scored higher on cognitive tests, had higher levels of physical activity,

and displayed more initiative and leadership than children supplemented with milk or plant-based foods (56, 57). An important caveat in the provision of meat supplements is that, in most resource-poor settings, animal source foods, except for eggs (58), are not readily available and are expensive. Even though the evidence for food supplements may be stronger than micronutrient supplements for effects on child development in children under two years of age, many of the micronutrient interventions published prior to the Larson and Yousafzai's meta-analysis (31) were under-powered to detect effects on child development. Since its publication, several other well-powered trials in at-risk populations have demonstrated significant effects of multiple micronutrients on early child development (28-30, 51). The findings from the Bihar trial add to this literature with an adequately powered randomized trial using MNPs in a malnourished population and finding effects on a range of cognitive functions using validated tools in infants and young children.

7.5.5 Leveraging Frontline Health Workers

Investigations into improving FLW workload and coverage are key to the sustainability of programs, such as the one piloted in Bihar. In India, the FLWS are called Accredited Social Health Activists (ASHAs). ASHAs are each responsible for an average of 150-200 households or a population of 1000. Their duties include promoting immunization, referrals for reproductive and child health, construction of toilets, raising awareness of health and its social determinants, including nutrition, sanitation and hygiene, healthy living and work spaces, existing health services, and family welfare services, and counseling on safe delivery, breastfeeding, complementary feeding, contraception, and prevention of infections. They also deliver nutritional supplements, chloroquine, disposable delivery kits, oral contraception, and condoms to households. Their workload is high and incentives are low. In fact, incentives are only provided for promoting universal immunization and for escorting pregnant

women for reproductive health services to the primary healthcare center (59). As such, most of the ASHAs' time is given to the latter two activities.

In Nepal, a study examining predictors of coverage of a similar MNP program to ours found that two variables were associated with coverage, namely attending a female community health volunteer-led meeting where MNPs were discussed and perceiving benefits of MNPs for the child (60). The study, however, warns that FLWs reported increased burden and authors suggest that attention needs to be given not to overburden the system (60). FLWs are often already burdened with a long list of activities, and with little incentive to add MNP delivery to their responsibilities, such a program is not sustainable. Further, long meetings are often not attended and little is derived from them. Short and clear messaging is necessary to any program, including MNP programs, and its delivery may require more than one model. For instance, a two-pronged approach may work in some cases, wherein FLWs are responsible for the initial message delivery and first time batch delivery, after which they may request that the local shop owner or other local volunteers help with subsequent deliveries of the product. In this way, the burden of repeated visits is alleviated. Government buy-in and potentially government investment, for instance to fund further incentives for FLWs, is required for the sustainability of such nutrition programs.

7.6 Limitations

The Bihar study had several general limitations, many of which were due to budget constraints, the purpose of the original parent study which was to examine impact on anemia and feeding practices, and the limitations imposed by fieldwork in rural India. There are three main limitations worth additional attention here: the use of a parent report to assess child development in the full sample,

missing measures of other important predictors of child development, the cross-sectional design at baseline and endline, and recording adverse events.

A more rigorous study that did not have the constraints of time and cost could have benefitted from using direct assessments of child language and personal-social development rather than, or in addition to, a parent report (i.e., the DMC-II). In the Bihar study, mothers from the intervention group were not blinded to the MNPs and, further, were educated on the benefits of MNPs. FLWs were instructed to discuss the advantages of using MNPs with mothers, including their benefit to cognitive development. So parents may have given biased responses because they wanted to fulfill our expectations of cognitive benefits and/or because they were more attentive to children's development than control parents. It is worth noting that memory and executive function, which were assessed using direct child assessments in a subsample of the children at endline only, showed no impact of the intervention. Had baseline measures of memory and executive function been available, difference-in-difference analyses may have led to different conclusions. Our results indicate that language and personal-social development (measured using the parent report), rather than memory and executive function, are truly responsive to an MNP intervention at this age, and/or that parent responses in the intervention group were biased towards positive results. In subsequent work, I would suggest using a direct child assessment measure in at least a subset of the children that could be used to validate the parent-report. The DMC-II has the option for direct observations, which could be added to validate the parent reports, although this takes additional time and expertise. Possible caregiver reporting bias could be examined by following process indicators on the program impact pathway, to examine whether child development findings correlate with more upstream indicators, such as MNP supply, delivery, and utilization.

Further, the measurement of other important predictors of child development, particularly maternal characteristics such as depression and anemia, could have added to our hypothesized

biopsychosocial model that examined the interconnection of multiple predictors of language, personal-social development, memory, and executive function. A more comprehensive model including maternal correlates may have demonstrated important associations, such as the contribution of maternal depression to psychosocial stimulation provided to the child at home, dietary diversity, and mental development.

Rather than using two cross-sectional surveys at baseline and endline, a follow up of the same children from baseline to endline would have permitted more thorough analyses into the pathways through which nutrition is acting on child development. For instance, a mediation analysis using longitudinal data could have been performed at the child-level to examine effects of the intervention on mental development through growth, hemoglobin, stimulation, and motor development. Using cross-sectional data limited our ability to examine these mediating factors. Further, because the age range (6-18 months) was the same at baseline and endline, and MNPs were only given starting at 6 months, those children included in the endline survey who were close to 6 months would not have had much opportunity to consume or benefit from MNPs. However, cross-sectional data allowed us to examine effects within an important age range when complementary feeding begins, and when home fortification with MNPs is likely to be used.

Lastly, recent concerns of possible harm from high-dose iron supplementation indicate that RCTs using iron need to do more to investigate potential negative effects. This can take the form of recording negative effects on cognition itself, and also on mediating factors, such as illness episodes and hospitalizations. Lozoff et al conducted a RCT with Chilean infants assigned to high or low or no iron groups at six months of age. At 12 months, children who did not receive iron had longer looking time on the Fagan test (less efficient information processing), crawled later, and scored lower on positive affect and social interaction than their counterparts who received iron (61). However, a follow up at 10 years of age indicated that the high iron group scored significantly lower than the low iron

group on spatial memory, arithmetic achievement, visual-motor integration, visual perception, and motor coordination (62). Other RCTs indicate that iron may promote infection. For instance, a large RCT in children 1-35 months of age living in Zanzibar were supplemented with iron and folic acid with and without zinc, or a placebo (63). Children who received iron were 12% more likely to die or need treatment in hospital for an adverse event and 11% more likely to be admitted to hospital. Amounts of iron in the Bihar trial were as high as those in the Zanzibari trial (12.5mg); however, the Data Safety and Monitoring Board of the Bihar trial did not find a reason to stop the study based on morbidity and mortality statistics throughout the study. An important challenge for future trials would be to examine potential harmful effects of iron using innovative techniques, such as gut microbiome testing. These results would be an important addition to the literature, particularly as iron supplementation programs scale up in varying contexts.

7.7 Strengths

The Bihar study also had several strengths worth emphasizing. For one, this was a large trial, adequately powered to detect an effect on motor and mental development of young children. It studied a population that had a potential to benefit from an intervention such as home fortification with MNPs. It also used the existing health infrastructure to further the evidence for the impact of large scale effectiveness trials on child development, an area that has not been examined extensively.

Further, this was a randomized trial which allowed us to compare results between intervention and control communities. Although not blinded, clustering of intervention groups by health sub-centers resulted in less contamination than if the intervention was assigned at the household level. Very few respondents from control communities reported receiving MNPs. The comparison group allowed us to attribute changes observed to the intervention itself.

Lastly, we used validated tools to measure various cognitive domains. We use a combination of parent report and behavioral measures to establish impacts of the intervention on, and predictors of, general mental and motor development scores in addition to specific cognitive functions (i.e., memory and executive function). These are cognitive functions that are not often studied in this age group in large population-based surveys in LMICs and therefore add substantially to the literature in this context.

Chapter 8: Conclusions

The child development findings from our Bihar study are an important contribution to the literature on correlates of motor, language, personal-social development, memory, and executive function, on mediators between nutrition and mental development, as well as on the effectiveness of a nutrition intervention using home fortification with MNPs on early child development in the context of Bihar, India. First, we add to the literature from a well-powered randomized trial using validated measures of child development. Second, we examine effects on child development using a combination of parent report and direct child assessments. The measurements used allow us to examine effects on, and correlates of, a variety of cognitive domains in a population and age group in which they have not been tested on such a large scale. Lastly, we contribute to the literature on pathways between nutrition and child development by examining mediation from nutritional, biological, stimulation, and household characteristics. Again, these pathways are examined for an array of cognitive functions.

Reviews of nutrition interventions have shown inconclusive effects on child development, specifically from micronutrients (31, 64-66). Yet, the significant findings from our Bihar trial, coupled with other recent MNP trials in similarly malnourished populations, point to the vulnerability of this age group and its potential to benefit from a simple and inexpensive intervention. Despite the

innovative measures used in the Bihar trial, the large sample size, and at-risk population, the study has important limitations (as outlined above). Concerns of harm from iron are also compelling. Based on these remaining limitations and concerns, there is still a need for more rigorous double blinded RCTs to examine the effects of multiple micronutrients on cognitive development of young children (67).

Lastly, I stress the need for more comprehensive approaches to improve child development. Cross-discipline collaboration between nutrition, environmental studies, psychology, and agriculture can achieve cost-effective and long-lasting solutions. As Black et al stated in the latest Lancet series on Early Childhood Development, there is an urgent need to expand multi-sectoral coverage of quality nurturing care, which encompasses health, nutrition, security and safety, responsive caregiving, and early learning and a political commitment and investment to do so (68).

Chapters 7 and 8 references

1. Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. The Lancet 2014.
2. Young MF, Mehta R, Gosdin L, Kekre P, Verma P, Larson L, Girard AW, Ramakrishnan U, Chaudhuri I, Srikantiah S. Impact of Home Fortification of Complementary Foods Program on Child Anemia and Stunting in Bihar, India. The FASEB Journal 2017;31(1 Supplement):165.7-.7.
3. International Institute of Population Sciences. NFHS-4 (National Family Health Survey-4) 2015-16: State Fact Sheet Bihar. 2016.
4. Friel JK, Aziz K, Andrews WL, Harding SV, Courage ML, Adams RJ. A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. The Journal of pediatrics 2003;143(5):582-6.
5. Rosado JL, Lopez P, Garcia OP, Alatorre J, Alvarado C. Effectiveness of the nutritional supplement used in the Mexican Oportunidades programme on growth, anaemia, morbidity and cognitive development in children aged 12-24 months. Public health nutrition 2011;14(5):931-7. doi: 10.1017/s1368980010003344.
6. Bornstein MH, Putnick DL, Lansford JE, Deater-Deckard K, Bradley RH. A Developmental Analysis of Caregiving Modalities Across Infancy in 38 Low- and Middle-Income Countries. Child development 2015;86(5):1571-87. doi: 10.1111/cdev.12402.
7. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. Journal of health, population, and nutrition 2010;28(1):23.
8. Singla DR, Shafique S, Zlotkin SH, Aboud FE. 25-element micronutrient powder benefits language but not cognition in Bangladeshi full term low birth weight children1. Journal of Nutrition 2014.
9. Honein MA, Paulozzi LJ, Mathews T, Erickson JD, Wong L-YC. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. Jama 2001;285(23):2981-6.
10. De Wals P, Tairou F, Van Allen MI, Uh S-H, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M. Reduction in neural-tube defects after folic acid fortification in Canada. New England Journal of Medicine 2007;357(2):135-42.
11. Erdogan MF, Demir O, Emral R, Kamel AN, Erdogan G. More than a decade of iodine prophylaxis is needed to eradicate goiter among school age children in a moderately iodine-deficient region. Thyroid : official journal of the American Thyroid Association 2009;19(3):265-8. doi: 10.1089/thy.2008.0253.
12. Jooste PL, Weight MJ, Lombard CJ. Short-term effectiveness of mandatory iodization of table salt, at an elevated iodine concentration, on the iodine and goiter status of schoolchildren with endemic goiter. The American journal of clinical nutrition 2000;71(1):75-80.
13. Obican SG, Jahnke GD, Soldin OP, Scialli AR. Teratology public affairs committee position paper: iodine deficiency in pregnancy. Birth Defects Research Part A: Clinical and Molecular Teratology 2012;94(9):677-82.
14. Anees M, Anis RA, Yousaf S, Murtaza I, Sultan A, Arslan M, Shahab M. Effect of maternal iodine supplementation on thyroid function and birth outcome in goiter endemic areas. Current medical research and opinion 2015;31(4):667-74.

15. Thilly CH, Swennen B, Moreno Reyes MR, Hindley J, Bourdoux P, Vanderpas J-B, Stanbury JB. Maternal, fetal, juvenile hypothyroidism, birthweight and infant mortality in the etiopathogeny of the IDD spectra in Zaire and Malawi. The damaged brain of iodine deficiency 1994:241-50.
16. Chaouki ML, Benmiloud M. Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. European journal of endocrinology 1994;130(6):547-51.
17. Zimmermann MB. The effects of iodine deficiency in pregnancy and infancy. Paediatric and perinatal epidemiology 2012;26(s1):108-17.
18. Banerjee A, Barnhardt S, Duflo E. Can Iron-Fortified Salt Control Anemia? Evidence from Two Experiments in Rural Bihar. National Bureau of Economic Research, 2016.
19. Baxter J, Zlotkin S. Compendium of Evidence on Double Fortified Salt. 2014.
20. Zimmermann MB, Zeder C, Chaouki N, Saad A, Torresani T, Hurrell RF. Dual fortification of salt with iodine and microencapsulated iron: a randomized, double-blind, controlled trial in Moroccan schoolchildren. The American journal of clinical nutrition 2003;77(2):425-32.
21. Andersson M, Thankachan P, Muthayya S, Goud RB, Kurpad AV, Hurrell RF, Zimmermann MB. Dual fortification of salt with iodine and iron: a randomized, double-blind, controlled trial of micronized ferric pyrophosphate and encapsulated ferrous fumarate in southern India. The American journal of clinical nutrition 2008;88(5):1378-87.
22. Martorell R, Ascencio M, Tacsan L, Alfaro T, Young MF, Addo OY, Dary O, Flores-Ayala R. Effectiveness evaluation of the food fortification program of Costa Rica: impact on anemia prevalence and hemoglobin concentrations in women and children. The American journal of clinical nutrition 2015;101(1):210-7. doi: 10.3945/ajcn.114.097709.
23. Bougma K, Aboud F, Lemma T, Frongillo EA, Marquis GS. Introduction of iodized salt improved infants' mental development in a community-based cluster randomised effectiveness trial in Ethiopia. British Journal of Nutrition Submitted.
24. Kramer M, Kumar S, Vollmer S. School Feeding, Iron-Fortified Salt and Child Cognitive Ability: Evidence from a Randomized Controlled Trial in Rural India. Unpublished.
25. Neufeld LM, Friesen VM. Impact evaluation of food fortification programs: review of methodological approaches used and opportunities to strengthen them. Edtion ed. In: Hurrel RaM, V., ed. Fortification in a Globalized World, forthcoming.
26. Grantham-McGregor SM, Powell CA, Walker SP, Himes JH. Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. Lancet 1991;338(8758):1-5.
27. Hoddinott J, Maluccio JA, Behrman JR, Flores R, Martorell R. Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults. Lancet 2008;371(9610):411-6. doi: 10.1016/s0140-6736(08)60205-6.
28. Prado EL, Abbeddou S, Yakes Jimenez E, Some JW, Ouedraogo ZP, Vosti SA, Dewey KG, Brown KH, Hess SY, Ouedraogo JB. Lipid-Based Nutrient Supplements Plus Malaria and Diarrhea Treatment Increase Infant Development Scores in a Cluster-Randomized Trial in Burkina Faso. The Journal of nutrition 2016. doi: 10.3945/jn.115.225524.
29. Prado EL, Adu-Afarwuah S, Lartey A, Ocansey M, Ashorn P, Vosti SA, Dewey KG. Effects of pre- and post-natal lipid-based nutrient supplements on infant development in a randomized trial in Ghana. Early human development 2016;99:43-51. doi: 10.1016/j.earlhumdev.2016.05.011.
30. Prado EL, Maleta K, Ashorn P, Ashorn U, Vosti SA, Sadalaki J, Dewey KG. Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi. The American journal of clinical nutrition 2016;103(3):784-93. doi: 10.3945/ajcn.115.114579.

31. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children under-two in low- and middle-income countries. Maternal & child nutrition 2017;13(1). doi: 10.1111/mcn.12229.
32. Larson LM, Prado E, Kubes JN, Ramirez Luzuriaga M, Shanjar A. Associations and effects of increased hemoglobin in infants and preschool children on growth, development and chronic disease: a systematic review and meta-analysis Unpublished.
33. Odle J, Jacobi SK, Boyd RD, Bauman DE, Anthony RV, Bazer FW, Lock AL, Serazin AC. The Potential Impact of Animal Science Research on Global Maternal and Child Nutrition and Health: A Landscape Review. Advances in nutrition (Bethesda, Md) 2017;8(2):362-81. doi: 10.3945/an.116.013896.
34. Aboud FE, Bougma K, Lemma T, Marquis GS. Evaluation of the effects of iodized salt on the mental development of preschool-aged children: a cluster randomized trial in northern Ethiopia. Maternal & child nutrition 2016. doi: 10.1111/mcn.12322.
35. Fernald LC, Kagawa RM, Knauer HA, Schnaas L, Guerra AG, Neufeld LM. Promoting child development through group-based parent support within a cash transfer program: Experimental effects on children's outcomes. Dev Psychol 2017;53(2):222-36. doi: 10.1037/dev0000185.
36. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, Jaeschke R. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology 2011;64(4):383-94.
37. Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol 2015;66:433-57. doi: 10.1146/annurev-psych-010814-015128.
38. Grantham-McGregor SM, Fernald LC, Kagawa RM, Walker S. Effects of integrated child development and nutrition interventions on child development and nutritional status. Annals of the New York Academy of Sciences 2014;1308:11-32. doi: 10.1111/nyas.12284.
39. Yousafzai AK, Obradovic J, Rasheed MA, Rizvi A, Portilla XA, Tirado-Strayer N, Siyal S, Memon U. 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. The Lancet Global health 2016;4(8):e548-58. doi: 10.1016/s2214-109x(16)30100-0.
40. Gowani S, Yousafzai AK, Armstrong R, Bhutta ZA. Cost effectiveness of responsive stimulation and nutrition interventions on early child development outcomes in Pakistan. Annals of the New York Academy of Sciences 2014;1308:149-61. doi: 10.1111/nyas.12367.
41. Organization WH. Prevention of Iron Deficiency Anemia in Adolescents: A Role of Weekly Iron and Folic Acid Supplementation. Geneva: World Health Organization 2011.
42. Sightandlife. Nutrition at the heart of the SDGs. Retrieved from http://www.sightandlife.org/fileadmin/data/Infographics/1_1_infograph_nutrition_at_the_heart_of_the_SDGs.pdf. Retrieved on April 3 2017: Sight and Life., 2017.
43. Fernald LCH, Kariger P, Engle P, Raikes A. Examining early child development in low-income countries. Washington DC: The World Bank 2009.
44. Ahun M. Maternal and child health and development in rural Ghana. Department of Psychology. Montreal, Quebec: McGill University, 2015.
45. Vinther T. Elicited imitation: A brief overview. International Journal of Applied Linguistics 2002;12(1):54-73.
46. deRegnier RA, Nelson CA, Thomas KM, Wewerka S, Georgieff MK. Neurophysiologic evaluation of auditory recognition memory in healthy newborn infants and infants of diabetic mothers. The Journal of pediatrics 2000;137(6):777-84. doi: 10.1067/mpd.2000.109149.

47. Tarullo AR, Obradovic J, Keehn B, Rasheed MA, Siyal S, Nelson CA, Yousafzai AK. Gamma power in rural Pakistani children: Links to executive function and verbal ability. Developmental cognitive neuroscience 2017;26:1-8. doi: 10.1016/j.dcn.2017.03.007.
48. Cusick SE, Georgieff MK. The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days". The Journal of pediatrics 2016;175:16-21. doi: 10.1016/j.jpeds.2016.05.013.
49. Pollitt E, Watkins WE, Husaini MA. Three-month nutritional supplementation in Indonesian infants and toddlers benefits memory function 8 y later. The American journal of clinical nutrition 1997;66(6):1357-63.
50. Nguyen PH, Gonzalez-Casanova I, Young MF, Truong TV, Hoang H, Nguyen H, Nguyen S, DiGirolamo AM, Martorell R, Ramakrishnan U. Preconception Micronutrient Supplementation with Iron and Folic Acid Compared with Folic Acid Alone Affects Linear Growth and Fine Motor Development at 2 Years of Age: A Randomized Controlled Trial in Vietnam. The Journal of nutrition 2017:jn250597.
51. Matias SL, Mridha MK, Tofail F, Arnold CD, Khan MS, Siddiqui Z, Ullah MB, Dewey KG. Home fortification during the first 1000 d improves child development in Bangladesh: a cluster-randomized effectiveness trial. The American journal of clinical nutrition 2017. doi: 10.3945/ajcn.116.150318.
52. Ali H, Hamadani J, Mehra S, Tofail F, Hasan MI, Shaikh S, Shamim AA, Wu LS, West KP, Jr., Christian P. Effect of maternal antenatal and newborn supplementation with vitamin A on cognitive development of school-aged children in rural Bangladesh: a follow-up of a placebo-controlled, randomized trial. The American journal of clinical nutrition 2017;106(1):77-87. doi: 10.3945/ajcn.116.134478.
53. Christian P, Morgan ME, Murray-Kolb L, LeClerq SC, Khatry SK, Schaefer B, Cole PM, Katz J, Tielsch JM. Preschool iron-folic acid and zinc supplementation in children exposed to iron-folic acid in utero confers no added cognitive benefit in early school-age. The Journal of nutrition 2011;141(11):2042-8. doi: 10.3945/jn.111.146480.
54. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutrition journal 2010;9:4. doi: 10.1186/1475-2891-9-4.
55. Stoltzfus RJ, Kvalsvig JD, Chwaya HM, Montresor A, Albonico M, Tielsch JM, Savioli L, Pollitt E. Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. Bmj 2001;323(7326):1389-93.
56. Neumann CG, Murphy SP, Gewa C, Grillenberger M, Bwibo NO. Meat supplementation improves growth, cognitive, and behavioral outcomes in Kenyan children. The Journal of nutrition 2007;137(4):1119-23.
57. Whaley SE, Sigman M, Neumann C, Bwibo N, Guthrie D, Weiss RE, Alber S, Murphy SP. The impact of dietary intervention on the cognitive development of Kenyan school children. The Journal of nutrition 2003;133(11 Suppl 2):3965s-71s.
58. Iannotti LL, Lutter CK, Bunn DA, Stewart CP. Eggs: the uncracked potential for improving maternal and young child nutrition among the world's poor. Nutr Rev 2014;72(6):355-68. doi: 10.1111/nure.12107.
59. Bajpai N, Dholakia RH. Improving the performance of accredited social health activists in India. Mumbai: Columbia Global Centres South Asia 2011.
60. Jefferds ME, Mirkovic KR, Subedi GR, Mebrahtu S, Dahal P, Perrine CG. Predictors of micronutrient powder sachet coverage in Nepal. Maternal & child nutrition 2015;11 Suppl 4:77-89. doi: 10.1111/mcn.12214.

61. Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003;112(4):846-54.
62. Lozoff B, Castillo M, Clark KM, Smith JB. Iron-fortified vs low-iron infant formula: developmental outcome at 10 years. Archives of pediatrics & adolescent medicine 2012;166(3):208-15. doi: 10.1001/archpediatrics.2011.197.
63. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet 2006;367(9505):133-43. doi: 10.1016/s0140-6736(06)67962-2.
64. Pasricha S-R, Hayes E, Kalumba K, Biggs B-A. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. The Lancet Global Health 2013;1(2):e77-e86.
65. Thompson J, Biggs BA, Pasricha SR. Effects of daily iron supplementation in 2- to 5-year-old children: systematic review and meta-analysis. Pediatrics 2013;131(4):739-53. doi: 10.1542/peds.2012-2256.
66. Wang B, Zhan S, Gong T, Lee L. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. The Cochrane database of systematic reviews 2013(6):Cd001444. doi: 10.1002/14651858.CD001444.pub2.
67. Larson LM, Phiri KS, Pasricha SR. Iron and cognitive development: what is the evidence? Annals of Nutrition and Metabolism In Press.
68. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, Lu C, McCoy DC, Fink G, Shawar YR, Shiffman J, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389(10064):77-90. doi: 10.1016/s0140-6736(16)31389-7.