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Early-life nutrition, child growth, and adult cognitive and socioemotional functioning in Guatemala

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# Abstract

Early-life nutrition, child growth, and adult cognitive and socioemotional functioning in Guatemala

By María José Ramírez Luzuriaga

Children that develop in safe and nurturing environments that provide adequate nutrition, psychosocial stimulation, and learning opportunities are better equipped to reach their full developmental potential. It is estimated that in low-and middle-income countries (LMICs), 43% of children under age five do not reach basic developmental milestones due to causes that are rooted in poverty. This dissertation uses extensive longitudinal data to explore long-term associations between early-life nutrition, psychosocial stimulation, and child growth on cognitive and socioemotional capacities in subjects 40 to 57 y of age who in early-childhood participated in a nutritional supplementation trial in eastern Guatemala. Specific aims were to 1) examine associations between exposure to nutritional supplementation in the first 1,000 days and adult executive function and socioemotional capacities, and identify mediators between enhanced early-life nutrition and adult socioemotional outcomes, 2) identify distinct height-for-age (HAZ) linear growth trajectories from birth through age 84 months and examine their predictors and associations with adult executive function and socioemotional capacities, and 3) determine the cross-sectional interrelationships between cognitive and socioemotional functioning in adulthood. Results indicated that exposure to nutritional supplementation in the first 1,000 days was positively associated with executive function and socioemotional capacities at ages 40 to 57 y (n=1,268). Mediation analysis showed stronger associations between psychosocial stimulation and cognitive abilities than between nutritional supplementation and cognitive abilities (n=1,640). Results from the second aim revealed that linear growth trajectories showed similar (parallel) slopes that were primarily distinguished as a matter of severity of linear growth faltering at birth (intercepts). Maternal height, socioeconomic status, and exposure to nutritional supplementation in the first 1,000 days were positively associated with membership to the high-HAZ linear growth trajectory. Linear regression models indicated a gradient of positive associations between HAZ trajectories and measures of cognitive ability and meaning and purpose at ages 40 to 57 y. Completed grades of schooling partially mediated the association between high-HAZ linear growth trajectory and scores on non-verbal fluid intelligence and working memory capacity. Lastly, the cross-sectional analysis indicated that executive function and non-verbal fluid intelligence at ages 40 to 57 y were strongly correlated with each other and weakly correlated with socioemotional functioning (n=1,268). Findings from this dissertation suggest that linear growth is a marker of early-life neurological development that remains intricately intertwined with both cognitive and socioemotional domains. Furthermore, results suggest that in populations in which undernutrition is prevalent, programs addressing both nutrition and psychosocial stimulation may produce greater long-term benefits in cognitive and socioemotional outcomes than nutritional supplementation alone. This study, together with several others conducted in LMICs, indicate the need to identify evidence-based and comprehensive intervention packages that integrate psychosocial stimulation and nutritional components in early childhood.

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**List of abbreviations**

| | |
|---|---|
| BIC | Bayesian Information Criterion |
| BLRT | Bootstrap Likelihood Ratio Test |
| CFA | Confirmatory Factor Analysis |
| CFI | Comparative Fit Index |
| DCCS | Dimensional Change Card Sort Test |
| GMM | Growth Mixture Modeling |
| HAZ | Height-for-age Z score |
| IDA | Iron deficiency anemia |
| INCAP | Institute of Nutrition of Central America and Panama |
| IQ | Intellectual quotient |
| LCA | Latent Class Analysis |
| LCGA | Latent Class Growth Analysis |
| LCGMM | Latent Class Growth Mixture Modeling |
| LMICs | Low-and-middle income countries |
| LMR-LRT | Lo-Medell-Rubin-Likelihood Ratio Test |
| MI | Modification Indices |
| NIH | National Institutes of Health |
| RMSEA | Root Mean Square Error of Approximation |
| RRR | Relative Risk Ratio |
| SEM | Structural Equation Modeling |
| SGA | Small for gestational age |
| SRQ-20 | Self-reported Questionnaire |

| | |
|---|---|
| STD | Standardized |
| TLI | Tucker-Lewis Index |
| WHO | World Health Organization |
| WHOQOL-SRPB | World Health Organization Quality of Life, Spirituality, Religiousness, and Personal Beliefs Questionnaire |
| WLSMV | Weighted Least Square Mean and Variance estimator |

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# CHAPTER 1: Introduction

Advances in neuroscience research indicate that the origins of adult health, social and emotional wellbeing are established in early childhood (1). Children that develop in environments that are safe, nurturing and provide adequate nutrition, psychosocial stimulation and learning opportunities are better equipped to reach their full developmental potential (2). It is estimated that in low-and middle-income countries (LMICs) 43% of children under age five do not reach basic developmental milestones in cognitive and socioemotional growth due to causes that are rooted in poverty (3).

The main domains of child development include physical, linguistic, socio-emotional and cognitive. Each enables and works in mutual coordination to support the development of the other but the exact link between these processes remains unclear (4). The physical domain includes the development of gross and fine motor skills and involves changes in linear growth and strength. The acquisition of language and oral communication skills occurs over time as children increase their vocabulary and their ability to put ideas into words. The socio-emotional domain includes the growth of a child in understanding and controlling emotions, establishing secure attachments with adults and interacting with others (4). The cognitive domain refers to the ability of the child to process thoughts, remember, hold adequate attention and follow simple instructions appropriate to age and experience. It comprises a set of cognitive skills collectively known as executive function, required for the control of thoughts and actions that facilitate the achievement of goals (5). Current models propose that executive function encompasses three interrelated core skills: working memory, inhibitory control, and cognitive flexibility (6). These core capacities start to develop in early childhood and provide the basis for a full range of executive function abilities that continue to develop throughout adolescence and early adulthood (e.g., understanding different points of view, organizing, regulating emotions, being self-aware).

Throughout this dissertation, the term cognitive development is used to define the child's cognitive processes in the first two years of life. Mental development encompasses both cognitive and language skills and is used interchangeably with cognitive and language development. Cognitive ability is used to define the various cognitive processes involved with language and higher reasoning skills throughout school-age and adulthood.

Adequate experiences and environments during the prenatal period and the first few years of life are crucial for optimal brain and child development. These include prenatal and postnatal nutrition (7), psychosocial stimulation (8-11), absence of toxins in the physical environment and maternal mental health (12).

Nutrition plays an important role in growth and brain development, especially during pregnancy and the first two years after birth. This period coined "the first 1,000 days" has been recognized as an important window of opportunity, where the effects of nutrition interventions are most effective. Randomized trials of nutritional supplements provided in the first two years of life to undernourished children living in poverty suggest causal links between child undernutrition, motor and mental development (13-15) and cognitive abilities (16-18). The long-term effects of early-life nutritional deficits have been documented in a series of follow-up assessments of the Institute of Nutrition of Central America and Panama (INCAP) Oriente Longitudinal Study (1969-77) in eastern Guatemala. These studies show that early-life nutritional supplementation in the first two years of life improved intellectual performance (16, 17), wages (19), schooling attainment and cognitive scores in reading, comprehension and intelligence tests (18), throughout adolescence, early and mid-adulthood.

Although associations between child undernutrition and cognitive abilities are well documented, the socioemotional consequences of early-life nutritional deficits are less well understood. The development of socioemotional skills occurs along with sensory-motor, cognitive, and language capacities and provides the basis for emotional wellbeing and adult socioemotional functioning and behavior. Longitudinal studies examining associations between early-life nutritional status and later behavioral outcomes show that children who were stunted or underweight in early-childhood show poorer social skills and attention, and more problems with conduct at school age than children of adequate nutritional status (20-22). Only a few nutritional supplementation trials have examined long-term effects on socioemotional outcomes with follow-up periods limited through age 8 years (20, 23, 24).

Recent academic debate has suggested that cognitive development may also respond to interventions post–1,000 days (2), and that linear growth retardation and stunting should not be the focus of interventions that aim to increase cognitive development because it is unlikely that a causal association exist between these two (25, 26).

In LMICs, short length- or height-for-age is one of the strongest correlates of poor cognitive and motor development (27, 28). Hence, many efforts are placed on assessing the effect of nutritional interventions on children’s height. Stunting, defined as height-for-age Z-score (HAZ) <-2 SD below a reference population, is a common indicator of chronic malnutrition that typically begins in utero and usually reflects persistent, cumulative effects of nutrition deficits and other environmental factors (29). Studies conducted in LMICs indicate that stunting in the first 1,000 days is negatively associated with later cognition, executive function, and school attainment. After 24 months, these associations are attenuated (27, 30). Some catch up in linear growth is possible after 24 months, with unclear cognitive gains (31, 32). An emerging body of evidence indicates that post-natal linear growth throughout the ages of 9 to 12 years is weakly associated with measures of language and math achievement at age 12 (33), and measures of cognitive and academic scores at ages 9 to 12 y (34).

Associations linking linear growth in early childhood with later socioemotional outcomes have received much less attention (27) partly because socioemotional measures are not routinely obtained in applied research, thus determinants have remained unknown. Moreover, although it is well established that short length-or height-for-age is one of the strongest correlates of poor cognitive development in LMICs, there is limited evidence on the association between linear growth throughout childhood and adult executive function and socioemotional capacities.

It is well established that cognitive and socioemotional capacities are intimately intertwined during early brain development. Each developmental domain enables and works in mutual coordination to support the development of the other. For instance, emotional wellbeing and social competence provide the basis for cognitive abilities to develop (4). However, little is known about how cognitive and socioemotional processes interrelate later in life, especially among populations living in poor-resource settings of LMICs.

This dissertation addresses gaps in the literature and adds to the current academic debate by examining the influence of early-life environments on cognitive and socioemotional outcomes in adulthood, with a focus on early-life nutrition. Using extensive longitudinal data this dissertation explores long-term associations between early-life nutrition, psychosocial stimulation and post-natal linear growth throughout childhood on cognitive and socioemotional capacities in a prospective cohort of Guatemalan adults who, in early-childhood, participated in a nutritional supplementation trial in four rural communities in eastern Guatemala. The aims of this dissertation are as follows:

### 1.1 Research Aim 1

*Examine associations between exposure to nutritional supplementation in the first 1,000 days and adult executive function and socioemotional capacities and identify mediators between enhanced nutrition in early-life and adult socioemotional outcomes.*

In this aim, regression models with double-difference estimates are used to examine associations between exposure to nutritional supplementation in the first 1,000 days and adult executive function and socioemotional capacities in 1,268 subjects at ages 40-57 y who had participated in a cluster-randomized nutritional supplementation trial in early-childhood. Also, the hypothesis that there may be psychosocial and cognitive mediators on the association between early-life exposure to nutritional supplementation and adult socioemotional outcomes is tested. To address this question, additional data collected during early-childhood and at ages 26-42 y is used to examine the longitudinal associations between early-life nutritional supplementation and adult socioemotional capacities through psychosocial stimulation, executive function and other cognitive abilities using Structural Equation Modeling (SEM) techniques (n=1640).

### 1.2 Research Aim 2

*Identify distinct height-for-age (HAZ) linear growth trajectories from birth through age 84 months and examine their predictors and associations with adult executive function and socioemotional capacities.*

In this aim, Latent Class Growth Analysis (LCGA) is used to examine longitudinal trajectories of height-for-age z-scores (HAZ) from 0 to 84 months in 1,499 subjects. Predictors of HAZ trajectories are examined using multinomial logistic regression models. Associations between HAZ growth trajectories and adult measures of cognitive and socioemotional functioning at ages 40-57 y are assessed using linear regression models. A mediation analysis is also conducted to test whether the estimated association between HAZ class membership on cognitive outcomes is mediated by completed years of schooling.

## 1.3 Research Aim 3

*Determine the cross-sectional interrelationships between cognitive and socio-emotional functioning in adulthood.*

In this aim, Structural Equation Modeling is used to examine cross-sectional intercorrelations between cognitive and socioemotional latent domains in 704 women and 564 men at ages 40-57 y, living in four rural communities in eastern Guatemala and Guatemala City. Studied domains include psychological wellbeing, spirituality and religion, emotional support, executive function, intelligence, and mental health. Confirmatory Factor Analysis (CFA) is used to examine whether the established dimensionality and factor-loadings patterns for latent domains fit our sample population.

The next chapter of this dissertation presents a literature review. Chapter 3 provides information about the study population, research setting, and methods. Chapter 4-6 are standalone manuscripts for publication in peer-reviewed journals, and Chapter 7 is a summary of the overarching findings and discussion of results, strengths, limitations and future directions.

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# CHAPTER 2: Background

A large body of evidence indicates that the origins of adult health, social and emotional wellbeing are established in early childhood (1). In the first few years of life, the child's brain develops at a faster rate than at any other period in development. Children brought up in safe and nurturing environments, that provide adequate nutrition, psychosocial stimulation and learning opportunities are better equipped to reach their full developmental potential (2).

## 2.1 A Life Course Approach to Adult Outcomes

The examination of associations between early-life exposures and adult cognitive and socioemotional outcomes requires the use of theoretical models that help clarify the different mechanisms through which individuals' trajectories interact with each other over time. Two well-known theoretical models proposed in the life course epidemiology literature are used throughout this dissertation: the sensitive period model, and the accumulation model.

The sensitive period model assumes that differences in adult outcomes observed across social groups are partly explained by exposures occurring in specific periods of development (3). Adverse exposures during sensitive periods of development (i.e., psychosocial deprivation, illness, malnutrition) have been associated with biological, cognitive, and psychosocial development during fetal life, infancy, and childhood. They could have the potential to cause irreversible damages to affected individuals (3). Other proposed sensitive periods that may be particularly important for social and emotional development include leaving the parental home, entry into the labor market, setting up one's residence, the transition to parenthood, and job insecurity (4).

The accumulation model proposes that life course exposure to adverse environmental and socioeconomic conditions and health behaviors throughout the life course accumulate over time. The accumulative risk model examines the sum of such adverse exposures on the individual's life and their influence on outcomes over time (3).

## 2.2 Early Brain Development

It is well documented that the interplay between genes and the environment determines the development of the brain (1). Genes direct brain growth by instructing the basic properties of nerve cells and providing the instructions for connecting nerve cells within and across circuits. The environment includes pre-natal and post-natal exposures, as well as conditions that arise during labor and delivery (1, 5).

The maturation of the central nervous system has been described to include six sequential and partially overlapping stages: dorsal induction, ventral induction, proliferation, migration, organization, and myelination. Disruption of any of these stages could result in miscarriages, clinical disorders, or the brain not reaching its full growth and developmental potential (6).

*Dorsal induction* takes place during the first month of gestation. It involves the folding back of the developing embryo forming the neural tube, which will eventually develop into the brain and spinal cord. On day 26 of gestation, the neural tube closes, marking the end of dorsal induction. *Ventral induction* occurs from weeks 4 to 10 of gestation. The cerebrum and the cerebellum are formed during this time. The cerebrum includes the cerebral cortex, - the outermost layer of the brain, responsible for most higher-order cognitive functions, and the cerebral medulla. The cerebellum located at the back of the brain stem plays essential functions in motor development, speech and coordination (5, 7). *Proliferation* starts from week 4 of gestation and involves the formation of neuroblasts that will eventually develop into neurons (the basic unit of the central nervous system), and glioblasts. More neuroblasts are produced at this stage than needed for a functional brain. Neuroblasts proliferate rapidly from 8 to 16 weeks of gestation. Glioblasts are also formed at this time, but their proliferation occurs approximately 5 to 12 months after birth. *Migration* starts from week 6 to 8 of gestation up to 8 months and involves the movement of neuroblasts and glioblasts to their final destination. During this process, neuroblasts transform into neurons and attach to the surface of the glial cells, which guide them to their final position. *Organization* starts at six months of gestation and continues after birth. At this phase, most neurons consist of a cell body, axons, and dendrites. The electrochemical communication between axons of sending neurons and dendrites of receiving neurons is called a synapse (5). Just like neurons, more synapses are produced at this stage than are needed for a functional brain. Following this period of neuron and synapsis overproduction, the brain undergoes a process of systematic pruning in which neurons that fail to make a connection are removed through apoptosis (8), and the neural connections that are left increase in speed and efficiency through myelination, the sixth and last phase of brain formation. *Myelination* starts at six months of gestation and continues into adulthood. Glial cells produce myelin, a fatty acid that coats axons allowing for rapid impulse transmission. Pruning and myelination are more prevalent in early childhood but continue throughout life (5, 7). For instance, the prefrontal cortex, the area of the brain responsible for the acquisition of executive function skills becomes fully myelinated around early adulthood (9).

A healthy full-term pregnancy provides the optimal environment for early brain development. As the neural circuits mature, environmental exposures can impact the chemical environment and electrical information of the circuit, modifying its architecture and genetic blueprint (10). These exposures include prenatal and postnatal nutrition, the amount and quality of psychosocial stimulation, and environmental conditions (e.g., bacteria leading to diarrhea or trachoma, or parasites leading to malaria) (11).

## 2.3 Stress and Early Brain Development

The links between early-life psychosocial adversities and developmental outcomes are well documented (7, 12). The mechanisms through which this operates seems to involve the prolonged activation of the stress response in the body. The stress response begins with the activation of the hypothalamic-pituitary-adrenocortical axis, which results in stress hormonal secretion from the adrenal gland (i.e., cortisol), and activation of the autonomic nervous system (11). This process activates the fight or flight response, triggering a cascade of orchestrated physiological changes (e.g., increased blood pressure and heart rate) that affect the cardiovascular and immune systems, regulation of glucose levels in the body and gene expression. When the stress response remains activated for significant periods (e.g., during severe malnutrition or chronic abuse), the resulting physiological responses could impair the development of neural connections, especially in the areas of the brain dedicated to higher-order skills causing lifelong repercussions (13).

It has been documented that undernutrition exposes the body to stress hormones (e.g., cortisol) (14, 15). Moreover, children living in poverty are usually more exposed to multiple stressors (e, g., domestic or community violence, poor social support, unresponsive parenting) (16). The higher the insults in early childhood, the greater the risk of developmental delays, and impairments in learning capacity, behavior, physical and mental health (13).

Research shows that when adverse experiences in early childhood are frequent, strong or prolonged such as during extreme poverty or frequent abuse, nurturing relationships with caregivers appear to buffer and even reverse against the detrimental effects of stress hormones on brain circuits (16).

## 2.4 Domains of Early Childhood Development

Infancy and early childhood are critical periods for physical growth, cognitive and socioemotional development. It is estimated that in low-and middle-income countries (LMICs) 43% of children under age five do not reach basic developmental milestones in cognitive and socioemotional growth (17), due to causes that are rooted in poverty.

Child developmental domains are categorized in different ways by different disciplines. A common classification includes physical, cognitive, linguistic and socioemotional. An important hallmark, regardless of the terms used to describe them, is that they do not develop or operate in isolation, as each enables and works in mutual coordination to support the development of the other. For instance, emotional wellbeing and social competence provide the basis for cognitive abilities to develop (18).

Although it is well established that cognitive and socioemotional capacities are intimately intertwined during early brain development (18), little is known about how cognitive and socioemotional processes interrelate later in life, especially among populations living in poor-resource settings of LMICs.

Moreover, although the development of socioemotional competencies provides the basis for emotional wellbeing and adult socioemotional functioning and behavior (19), it has received less attention relative to sensory-motor, cognitive, and language capacities. Thus, predictors remain poorly understood.

### 2.4.1 Physical Development

The physical developmental domain involves changes in body size, muscle strength, and the development of gross and fine motor skills. It is through motor development that children can make purposeful movements, learn about the self, and explore the environment, promoting the further acquisition of cognitive and socioemotional capacities (20).

Adequate linear growth is an indicator of child health and a well-known determinant of childhood morbidity and mortality (21). Short length- or height-for-age primarily results from inadequate nutrition and infection (21, 22), and is one of the strongest correlates of poor cognitive and motor development in LMICs (23, 24). Stunting, defined as height-for-age z-score (HAZ) < -2 SD below a reference population, is a common indicator of chronic malnutrition that typically begins in utero and usually reflects persistent, cumulative effects of nutrition deficits and other environmental factors (25). In developing countries, 50% of children by age 2 years are stunted (26).

Studies in LMICs consistently show that stunting in the first 1,000 days associates with later cognition, executive function, and school attainment. When stunting occurs after the first 1,000 days, these associations are attenuated (23, 27). One of the proposed mechanisms linking stunting to reduced mental development suggests that it is through reduced motor activity that the child's ability to explore the environment and receive psychosocial stimulation gets limited (23). However, despite consistent associations between stunting and mental development, recent academic debate has pointed to the fact that it is unlikely that a causal association exists between them. Rather, physical growth is thought to be a marker of the inadequacy of the environment in which children developed (28).

### 2.4.2 Language Development

Language skills develop over time as children increase their vocabulary and their ability to put ideas into words (29). The quality and quantity of maternal speech are particularly important for promoting child language capacities and their ability to establish relationships between words (30, 31). Individual variation in early language acquisition seems to be explained by differences in early-life exposures and linguistic inputs from the environment (18). Longitudinal studies suggest that the development of oral language skills has important implications for learning and later academic achievement (32, 33). For instance, it has been documented that children with higher oral-language skills acquire new language, literacy, and reading skills faster than children with poorly developed oral language capacities in early-life (34, 35).

### 2.4.3 Cognitive Development

Cognitive development refers to the child's ability to process thoughts, remember, hold adequate attention, and follow simple instructions appropriate to age and experience (18). Furthermore, it includes the acquisition of higher-order skills required for planning and executing goal-oriented activities. These processes fall under the umbrella of "executive function." A well-accepted classification among psychologists proposes that executive function is comprised of three interrelated core skills; working memory, inhibitory control, and cognitive flexibility (36).

Working memory is the ability to hold short-term information from multiple sources, connect that information, and use it for everyday activities (37, 38). Working memory gradually develops over time. By 6 months of age, infants are able to retain information despite distraction (39). Studies show that the development of working memory capacity starts in the first year of life and continues at least into adolescence (38), with alternating periods of rapid and more stable growth. The first spur is between the ages of 2 and 8 years (40-43). Working memory capacity continues to improve over time and remains relatively stable throughout adolescence and early adulthood (44, 45). Results from magnetic resonance imaging (MRI) studies show that the regions of the brain involved in working memory tasks are the same in children and adults (46). In adults, however, the neural circuits in those brain regions are more efficient (47). The development of working memory capacity is associated with mathematic and reading skills and overall academic achievement (48, 49). Conversely, children with low working memory capacity are at higher risk of poor academic performance (50, 51).

Inhibitory control, also referred to as “inhibition” is the skill used to suppress dominant and unproductive responses, distractions or temptations. It permits to override habits, to think before taking action, and makes possible focused, selective, sustained attention and action (38). The ability of simple response inhibition develops during infancy. Complex response inhibition develops between the ages of 3 to 5 years, reaching its most rapid increase between the ages of 5 and 8 years of age (52). Longitudinal studies indicate that inhibitory control predicts adult outcomes. Results from a cohort of New Zealand children followed from birth to age 32 years show that childhood self-control predicted better physical and mental health, wealth, reduced jailtime and substance use (53).

Cognitive flexibility, also known as “shifting” is the ability to switch thinking and adjust it in response to the environment. It also entails thinking about multiple concepts simultaneously, approaching problems in different ways, or use different strategies until a specific task is accomplished (38). The development of cognitive flexibility emerges later in development, at about age 4 (54), and builds on working memory capacity and inhibitory control (38, 55). Cognitive flexibility significantly influences children’s social competence and academic achievement. For instance, early-childhood interventions that focus on cognitive flexibility result in significant increases in reading comprehension (56).

More complex executive function skills such as planning and organizing continue to develop throughout adolescence and early adulthood and require the simultaneous use of basic executive function skills (i.e. working memory, inhibitory control, and cognitive flexibility) (38).

Early-life cognitive self-regulation (the orchestration of executive function skills to determine behavior) has been shown to significantly contribute to later cognitive development, school readiness, and socioemotional functioning (1). It has been documented that children with higher levels of cognitive self-regulation, (including working memory, inhibitory control, and cognitive flexibility) score higher on tests of literacy, language, and mathematical abilities (57).

### 2.4.4 Socioemotional Development

The development of socioemotional skills occurs along with sensory-motor, cognitive, and language capacities and provides the basis for emotional wellbeing, and adult socioemotional functioning and behavior (19). However, relative to other developmental domains, it has received less attention and predictors remain poorly understood (11).

Socioemotional development has been described as a multidimensional construct that involves the ability of the child to understand, recognize, and manage emotions and behaviors. It also entails the ability to develop empathy for others and establish relationships with adults and peers (18). The development of socioemotional competence has been proposed to include elements of self-awareness, self-management, social awareness, relationship skills, and responsible decision-making (18). However, a general agreement on how to categorize this area of development is lacking (58). Moreover, measures of socio-emotional competencies in early childhood are usually not applied in research (11).

The development of social and emotional competencies starts in early childhood with caregiver-child interactions. Secure attachment is a well-known capability acquired in the first 2 years of life that has been recognized as essential for healthy socioemotional development (59).

It involves the ability of the child to derive emotional security from adults under stressful situations, (e.g., presence of a strange object or people). Securely attached children show minimal stress hormone activation when frightened by a strange event, relative to non-securely attached children (60). Moreover, studies show that securely attached children develop greater social skills (61, 62), exhibit higher cognitive, language development and school readiness throughout childhood relative to non-securely attached children (63). Moreover, securely attached children show minimal stress hormone activation when frightened by a strange event, relative to non-securely attached children (60). Furthermore, evidence from animal studies suggest that the quality of maternal-child interactions influences gene expression in areas of the brain involved in social and emotional function, leading to changes in brain structure (64-66), with long-term influences on physical and emotional stress regulation (67).

The development of socioemotional competence has important effects for early school adjustment and academic achievement (68-70). Socioemotional skills give children the possibility to engage in academic tasks through constructive and collaborative interaction with others, allowing them to dedicate sustained attention to learning from educators and peers (70). Studies assessing the relationships between poor socioemotional development and later behavioral outcomes consistently show that children with persistent early socioemotional delays experience more problems socializing, and adjusting to school, and work (71).

The links between malnutrition and behavior have also been documented. Studies show that undernourished children score lower on measures of secure attachment than well-nourished children (72, 73). Furthermore, longitudinal studies examining associations between early-life nutritional status and later behavioral outcomes show that children who were stunted or underweight in early-childhood show poorer social skills and attention, and more problems with conduct at school age than children of adequate nutritional status (74-76). A study examining associations between early-life nutritional status and personality profiles in adulthood (n=134) showed that participants who experienced severe malnutrition in the first year of life exhibited more anxiety, lower sociability, a lower sense of self-efficacy and less intellectual curiosity than non-malnourished peers at ages 37-43 years (77).

Proposed mechanisms for the association between early-life nutrition and socioemotional outcomes suggest that early-life nutritional deficits compromise the child's ability to engage with the environment and respond to stimulation, leading to less responsive interactions with caregivers (78-81). Additionally, it has been proposed that an undernourished child is often more irritable and withdrawn, causing caregivers to treat them with less sensitivity, resulting in altered patterns of brain development (82).

Only a few nutritional supplementation trials have examined long-term effects on socioemotional outcomes with follow-up periods limited to school age (74, 83, 84). In Guatemala, the hypotheses that malnutrition would be associated with specific aspects of social and emotional functioning was tested in 139 children at ages 6 to 8 years, who in early childhood participated in a nutritional intervention trial. Children were examined in free-play peer interaction and several tasks (i.e., group problem solving, construction activities with clay, competitive games, and impulse-control situations). Results controlling for socioeconomic characteristics indicated that children who received higher levels of nutritional supplementation prenatally, -through maternal supplementation during pregnancy, and from birth to age 2 years, showed more social involvement, more interest in the environment, and were more active and capable of showing positive and negative affective expression. Furthermore, these children were rated as more energetic and self-confident and were less frequently timid or anxious than children who received less supplementation (83, 84). The examination of the long-term effects of early-life nutritional supplementation trials on socioemotional outcomes into adulthood has not been conducted.

### 2.5 Predictors of Child Developmental Potential

Conditions that disrupt healthy brain development are directly associated with child developmental potential, that is, the ability of the child to think, learn, understand and follow directions, communicate and relate with others, control aggression, and solve problems appropriate to age and stage of maturity (11).

Factors that have been identified as predictors of brain development include a healthy full-term pregnancy, birth weight, adequate prenatal and postnatal nutrition, the amount and quality of psychosocial stimulation offered to the child, maternal mental health, environmental exposures (e.g., bacteria, parasites, toxins) and linear growth.

Linear growth is thought to be causally related to cognitive development, but recent academic debate has pointed to the fact that this may not be the case (28). Path analyses using data from four cohorts in LMICs show that out of 42 risk factors for cognitive development and linear growth at 18 months, only dietary diversity, hemoglobin concentration and size at birth predicted both cognitive and linear growth outcomes (85, 86). Linear growth was found to be more strongly predicted by maternal characteristics during pregnancy and diarrhea incidence, whereas cognitive development was found to be more strongly predicted by psychosocial stimulation. These findings suggest that factors that restrict growth potential and cognitive development partially overlap.

### 2.5.1 Nutrition

Adequate nutrition is essential throughout the lifespan, but it is especially important during pregnancy and the first two years of life, an important period for development that has been coined “the first 1,000 days”. Practices known to support healthy development embedded in the first 1,000 days include exclusive breastfeeding from birth to 6 months, and prolonged breastfeeding (along with nutrient-dense and dietary diverse complementary foods) up to age two years or beyond (87). Correlational studies suggest that breastfeeding influences better mental development (88). The most prominent breastfeeding study consists of a cluster-randomized trial of clinics in Belarus. Clinics were randomized to receive an intervention on breastfeeding counselling versus standard care. Results showed that rates of breastfeeding were higher among mother-child pairs in intervention clinics. School-age children (ages 6 years) from the intervention clinics had higher IQ scores and ratings of writing and reading ability (89).

Observational studies consistently show that nutritional deficits in the first 1,000 days result in impaired growth and cognitive development with long-lasting effects in social and human capital attainment (90). Furthermore, randomized trials of food supplements provided during critical age periods to undernourished children living in poverty suggest causal links between child undernutrition, motor and mental development (91-93), and later cognitive abilities (94, 95). However, although it is well accepted that nutritional deficits in the first 1,000 days have short, medium, and long-term effects on cognitive abilities, the socioemotional consequences of early-life nutritional deficits remain poorly understood.

Proposed mechanisms of the association between nutrition and mental development include reduced motor activity, psychosocial stimulation, and changes in brain structure and function as possible mediators (96-98). One proposed mechanism suggests that better nutrition influences gross motor skills such as the ability to crawl or walk at an earlier age, which indirectly allows the child to access more psychosocial stimulation through the exploration of the environment. However, the current evidence on the association between early walking and mental development does not support this claim (99). Another proposed mechanism suggests that better nutrition leads to increases in linear growth, which indirectly results in more sophisticated stimulation from caregivers. This mechanism rests on the notion that caregivers will treat children differently depending on their height, which could be non-applicable in populations where most children are small. Lastly, an additional proposed mechanism that has gained more credibility in recent years suggests that nutrition could have the potential to change brain structure. This notion is supported by a small but influential number of studies assessing the effects of nutritional exposures on brain development using electroencephalograms. Overall, these studies show that iron-deficient (100, 101), and formula fed children (102), show greater delays in brain activation to sensorial inputs than breast-fed children at ages 6 to 24 months.

Most evidence linking nutrient deficiencies to brain development during pregnancy and infancy comes from animal studies. Evidence from human populations originates from studies conducted in LMICs where nutritional deficiencies are prevalent, or from studies of natural experiments such as famines.

The extent to which nutrient deficiencies during pregnancy and early childhood affect brain function is not yet clear, as effectiveness studies conducted in this area of research have been limited. The most studied nutritional exposures on mental development include protein-energy malnutrition, fatty acids, iron, iodine, zinc, choline, and B-vitamins (97).

*2.5.1.1 Protein-energy Malnutrition*

Protein-energy malnutrition has been associated with neurodevelopmental disruptions. Autopsy studies using magnetic resonance imaging in infants with intrauterine growth retardation or severe acute malnutrition indicate fewer brain cells and dendritic growth compared to a healthy weight, well-nourished children (103-105). Moreover, studies using magnetic resonance technology indicate that adults who as infants were exposed to famine in utero show signs of brain lesions produced by the loss of myelin and axons (106).

Randomized trials of food supplements (with different combinations of energy, macronutrients, and micronutrients) offered during gestation and early childhood in poor-resource settings of LMIC suggest causal links between nutritional deficits on physical, cognitive and socioemotional outcomes. In Guatemala, maternal and child supplementation with high protein and energy vs. low energy and no protein (both supplements with an equal concentration of micronutrients) show positive associations on vocabulary, reading comprehension, and tests of math and general knowledge at ages 11 to 24 years (107). Also in Guatemala, nutritional supplementation in early childhood has been associated with child growth in the first 36 months of life (108), increased schooling attainment in women, higher IQ scores in both sexes (95), and increased earnings in men at ages 25 to 42 years (109). In Colombia, the provision of food baskets to poor resource families throughout pregnancy up to age 3 years resulted in higher scores on Griffith developmental quotient at age 3 years and reading skills at school age (110). In Indonesia, children in daycare centers provided with protein and energy snacks (vs. children not provided with snacks) showed higher motor scores at ages 9 to 23 months (111), and scored higher on tests of working memory capacity at ages 8 to 9 years (112).

Only a few food supplementation trials have examined long-term effects on socioemotional outcomes with follow-up periods limited through age 8 years (74, 83, 84). In Guatemala, children who received higher levels of nutritional supplementation prenatally (through maternal supplementation during pregnancy), and from birth to age 2 years, showed more social involvement and interest in the environment, were more active and capable of showing positive and negative affective expression at school-age. Furthermore, these children were rated as more energetic and self-confident and were less frequently timid or anxious than children who received less supplementation (83, 84).

#### *2.5.1.2 Fatty Acids*

Fatty acids are required during neurogenesis and as structural components of myelin. Animal studies show reduced neuron proliferation and altered composition of myelin in rodents with prenatal and postnatal fatty acid deficiency (113, 114). Long-chain polyunsaturated fatty acids, particularly n-3 fatty acids, are present in breastmilk and the brain; thus, their influence on mental development has been explored. In Mexico, a randomized controlled trial of docosahexaenoic acid supplementation during pregnancy showed benefits in birth weight and head circumference of offspring at delivery (115), and increased scores on tests of attention at age 5 years (116), but no effects on other key developmental domains.

*2.5.1.3 Iron*

Iron deficiency is a common nutrient deficiency worldwide and assumed to cause half of all causes of anemia (117). It has been documented that iron deficiency anemia (IDA) during infancy associates with fatigue and lower motor, cognitive, and behavioral function (118-121). These early differences seem to persist beyond infancy. Longitudinal studies show that adolescents who had IDA during infancy continue to score poorly than their non-anemic peers in tests of cognitive function and attention, and report more behavioral problems than their non-anemic peers during adolescence (122).

The provision of lower doses of iron in low-and middle-income populations, where the prevalence of iron deficiency is high, indicates positive effects on motor and mental development, socio-emotional development, and language capacities (122). In Nepal, a randomized trial of supplementation with iron, folic acid and vitamin A in pregnant women showed that children of mothers that received multiple micronutrients (iron, folic acid, and vitamin A) scored better on cognitive tests of non-verbal intelligence and executive function at ages 7 to 9 years than those that only received vitamin A (123).

*2.5.1.4 Iodine*

Iodine is an important constituent of thyroid hormones. It is estimated that 35% of the world population have insufficient iodine intake. Iodine deficiency is associated with hypothyroidism and intellectual disability (124, 125). Studies in iodine-deficient areas in China have shown reduced brain weight and no myelination at months 6 to 8 of gestation (126). Moreover, observational studies indicate associations between iodine deficiency and lower scores on IQ tests (127, 128). Follow-up assessments of iodine supplementation trials during the first and second semester of pregnancy indicate decreased neurological problems and higher cognitive scores in school-age children relative to supplementation in late pregnancy or after birth (129, 130).

*2.5.1.5 Zinc, Choline, and B-vitamins*

Zinc plays a significant role in DNA synthesis, cell division, and modulation of synapse function (131). In animal studies, zinc deficiency causes deficits in attention, learning, and memory (132). However, evidence from randomized trials of zinc supplementation during pregnancy in human populations show no effects on mental and motor development during childhood (133, 134).

Choline is required for stem cell proliferation and cell division. Also, acetylcholine, an important neurotransmitter, is synthesized from choline. In animal studies, choline deficiency during gestation shows long term effects in cholinergic function (135). Studies of choline supplementation in human populations have not been conducted.

Vitamin B12 deficiency is associated with neural tube defects (136). In animal models, gestational and postnatal B6 deficiency results in decreased dendritic branching (137), reduced myelination (138), and decreased synaptic density (139). Studies of B-vitamins supplementation alone and not as part of other micronutrients in human populations have not been conducted.

### 2.5.2 Psychosocial Stimulation

Psychosocial stimulation refers to external inputs (i.e., objects or events) that produce a psychological and physiological response in the child. The essence of psychosocial stimulation is observed in the interactions of the child with caregivers, particularly with the mother (11). If child-caregiver interactions are unresponsive, unreliable, or inappropriate, the developing brain fails to receive the stimulation it needs. Moreover, the body stress response activates, potentially exposing the developing brain with stress hormones.

Psychosocial stimulation in early childhood is often measured using the Home Observation for Measurement of the Environment (HOME) Inventory (140). Studies in LMICs have consistently reported strong and positive correlations between HOME scores and child mental development (141-143). The links between psychosocial stimulation, cognitive, and socioemotional development have also been examined longitudinally. The most prominent study consists of follow-up assessment of an early-childhood intervention provided to stunted children in Jamaica, documenting higher cognitive performance at school age (144), and fewer symptoms of depression, social inhibition, and reductions in violent behavior in early adulthood among those that were exposed to early psychosocial stimulation at ages 9 to 24 months (145).

Moreover, studies comparing institutionalized vs. non-institutionalized children, show that those who experienced conditions of severe neglect in orphanages shortly after birth show substantial decreased brain activity relative to children who were never put into orphanages (146).

A recent meta-analysis examining the effects of early-life interventions on child growth and cognitive development found that interventions promoting responsive care and learning opportunities had considerably larger effects on children's cognitive, language, and motor development than nutritional supplementation interventions (range effect sizes 0.38-48 vs. 0.05-0.08) (147).

### 2.5.3 Stunting

Short length- or height-for-age is one of the strongest correlates of poor cognitive and motor development in low-and middle-income countries (LMICs) (23, 24). Longitudinal studies examining associations between nutritional deficits in the first 1,000 days and later cognitive outcomes generally show that children who were stunted or underweight in early-childhood show reduced cognitive function, schooling achievement (90, 148), attention problems (149), than children of adequate nutritional status. However, despite consistent associations between stunted growth and cognitive development, recent academic debate has pointed to the fact that linear growth retardation and stunting should not be the focus of interventions that look to increase child mental development because it is unlikely that a causal association exist between these two (28, 150).

These arguments have been influenced by: First, the implausibility, based on current understandings, of the proposed pathways linking stunting to developmental delays. For instance, stunting is thought to be associated with reduced gross motor activity, limiting the child's ability to explore the environment and receive psychosocial stimulation (23), and thus reducing opportunities for the development of socioemotional and cognitive capacities (151). However, studies suggest that the attainment of gross motor skills is largely independent of variations in linear growth (152), while other studies show that the ability to walk at an earlier age has no association with mental development (99). Second, findings from path analysis studies with data from several cohorts in LMICs suggesting that predictors of cognitive development and height-for-age scores are only partially shared (85, 86, 153). Third, an emerging body of evidence shows that post-natal linear growth throughout the ages of 9 to 12 years is weakly associated with language and math achievement at age 12 years (154), and measures of cognitive and academic scores at ages 9 to 12 years (155).

Associations linking stunting in early childhood with later socioemotional outcomes have received much less attention (23), partly because socioemotional measures are not routinely collected in applied research. Moreover, although studies have shown that stunting is associated with later cognitive abilities, the extent to which post-natal linear growth patterns throughout childhood associate with adult cognitive and socioemotional functioning has not been explored.

## 2.6 Summary

Adequate nutrition in the first few years of life is crucial for optimal brain and child development. There is ample evidence on the cognitive consequences of early-life nutritional deficits. Observational and experimental studies consistently show that stunting in early childhood, specifically in the period between a woman's pregnancy and a child's second birthday associates with poor cognitive development, decreased schooling, and lower language and cognitive skills throughout adolescence and adulthood. There is limited research on the adult socioemotional consequences of early-life undernutrition. Only a few nutritional supplementation trials have examined long-term effects on socioemotional outcomes with follow-up periods limited to school age. Overall, these studies show that children that received nutritional supplementation in early life have more social involvement, more interest in the environment than non-supplemented children at school-age. Moreover, although it is well established that short length-or height-for-age is one of the strongest correlates of poor cognitive development in LMICs, there is limited evidence on the association between linear growth throughout childhood and adult executive function and socioemotional capacities. The proposed study investigates these gaps.

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# CHAPTER 3: Methods

## 3.1 Study Setting: The INCAP Longitudinal Study

The Institute of Nutrition of Central America and Panama (INCAP) Longitudinal Study is one of the richest sources of information about the importance of early-life nutrition for growth, development, and human capital in developing countries (1). The study consisted of a community-randomized, food supplementation trial implemented between 1969-1977 in four rural villages in eastern Guatemala.

The main purpose of the nutritional trial was to assess the effect of improved nutrition on the mental development of preschool children (2). Two-pairs of villages matched by population size were chosen from a pool of 300 communities. Matched villages had comparable socioeconomic characteristics and similar health indicators. At the time of the study design, average family incomes were very low (< $300 US per year), most adults were illiterate and moderate malnutrition and infectious diseases were endemic in all villages (3). One village from each pair was randomly chosen to receive a nutritious supplement "*atole*", and the other two villages received a control drink called "*fresco*" (2). *Atole*, a hot thick drink widely consumed in Guatemala contained 11.5 grams of protein and 163 kilocalories per cup (180 ml). The control drink *"fresco"* was a refreshing drink that contained no protein and 59 kilocalories per cup (180 ml). Both drinks contained micronutrients in equal concentration. Each supplement was provided free of charge to all residents of the village in a supplementation center twice a day, in mid-morning and mid-afternoon.

Attendance was open to all villagers but only pregnant or lactating women, and all children from birth up to age 7 years were included in the trial (2, 4). The final sample size for children consisted of 2,392 individuals born between 1962 and 1977.

There have been several waves of fieldwork involving the INCAP cohort since the original intervention study ended in 1977 (1). A description of data collection methods from the nutritional trial and follow-up waves relevant to this dissertation are presented as follows.

## 3.2 Data Sources

### 3.2.1 INCAP Nutrition Supplementation Trial 1969–77

Data were collected longitudinally in pregnant and lactating women and children 0-84 months. Collected information included census data, supplementation intake, home diet, anthropometry, morbidity, and mental development. A detailed description of all the measurements taken and operating procedures of these data are presented elsewhere (5).

#### *3.2.1.1 Supplementation Intake*

Measurements of supplementation intakes and attendance began on January 1st or May 1st, 1969 in large and small villages respectively, until February 28th, 1977 in all villages. The supplement was poured into cups (180 ml), which were refilled as often as requested. The amount of supplement intake was measured by recording the number of cups given to each participant (i.e., pregnant and lactating women and children 0-84 months) and subtracting any supplement leftover to the nearest 10 ml (2).

Early studies in this population assessing the influence of nutritional supplementation on outcomes of interest used individual supplement intakes as the independent variable. In the 2002-04 follow-up study, innovative techniques were implemented to improve the estimation effects of the nutritional intervention on outcomes of interest, taking advantage of its experimental design. These methods involved measuring exposure to nutritional supplementation rather than actual intakes.

*3.2.1.2 Exposure to Nutritional Supplementation*

The ages and periods at which children were exposed to the nutritional intervention varied across participants. The primary interest in this dissertation was to capture exposure to nutritional supplementation in the first 1,000 days. That is, exposed from conception through maternal supplementation during pregnancy, and from the child's own consumption from birth through age 2 years. Characterization of exposure to nutritional supplementation was based on the child’s date of birth and dates for which *atole* or *fresco* supplementation was offered in the villages.

Dummy variables for age of exposure to nutritional supplementation (i.e., *atole* or *fresco*) were created using two categories (i.e., fully exposed in the first 1,000 days, and partially or not exposed in the 1,000 days), and three categories (i.e., fully exposed in the first 1,000 days; partially exposed in the first 1,000 days, and not exposed at all in the first 1,000 days).

The interaction term between treatment assignment and age of exposure to nutritional supplementation provides a difference-in-difference (DD) estimator which captures the differential effect of the intervention in children exposed to *atole* relative to *fresco* in the first 1,000 days. The first difference compares the average change in the outcome across children exposed to *atole* in the first 1,000 days relative to *fresco*. The second difference subtracts the average change in the outcome across village treatments outside the first 1,000 days window.

#### *3.2.1.3 Anthropometry*

Trained anthropometrists measured height and length to the nearest 0.1cm using standardized protocols and procedures that remain widely used today (6). Maternal height was measured once, and child length was measured at or near 15d, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 60, 72, and 84 months using length boards.

The precision and reliability of measures were closely monitored throughout the study (7). Measures with two standard deviations from the age-specific means were retaken and calibration of instruments was conducted weekly. Frequent standardization exercises were held for anthropometrists (2).

#### *3.2.1.4 Socio-cultural, Economic and Environmental Characteristics*

Various socio-cultural and environmental variables were routinely collected and tested to determine which ones were more predictive of a child's mental development. These measures were obtained from repeated annual interviews and derived from a body of interviews and observational data collected on each child's family. These initial measures were sought to represent a composite picture of the family during the period of their collection. They included information on family composition, child-rearing practices, family and community relationships, social status, migration, patterns of communication, social competence, socialization processes, and economic aspects (5). Among these measures, was "task instruction" a rating that was conceived as an indicator of the parents' efforts to provide adult modeling and purposeful learning opportunities. This rating involved the assessment of the interaction of caregivers and siblings with the child in teaching the child to count, teaching him to do household tasks, and accompanying him to a nearby town.

Also, information on maternal characteristics, including completed grades of schooling and maternal age at respondents' birth was obtained by interview. Information on socioeconomic status was obtained from village censuses conducted in 1967 and 1975 of household characteristics and consumer durable goods measured in participant households. To capture early-childhood household socioeconomic status a single combined score was created using principal components analyses (8). The 1967 index score was used for participants born before 1971, and the 1975 index score was used for those born after 1970.

#### *3.2.1.5 Additional Measures Collected Cross-sectionally (1974-1975)*

An instrument designed to measure the amount and type of social and intellectual stimulation received by the children in their home environments was applied during late 1974-1975 for a study in collaboration with the RAND Corporation. A composite score was derived from these measures including number, condition, and material of toys, interaction with caregivers, number of walls in the room which have picture or sketch and presence of books at home. More than 50% of the questions assessed caregiver-child interactions. Additional details are provided elsewhere (9).

3.2.2 Human Capital Study 2002-2004

The objective of this study was to explore the impact of early childhood nutrition on adult human capital formation and economic productivity. By, 2003 participants were 26-42 years of age; most had finished schooling, were married, and had chosen an occupation. A comprehensive assessment of educational attainment was obtained by interview, including the highest grade of formal and informal education completed. Informal education consisted of literacy programs that were available in Guatemala for adults who wished to complete primary or secondary school. Tests of intelligence were assessed with the Raven's Progressive Matrices test (sets A, B, and C), a non-verbal fluid intelligence (10). Additionally, all literate participants were administered the Interamerican Series test of Reading Comprehension and Vocabulary. Additional measures included labor force participation and income, household expenditure, wealth, marriage and reproductive history.

The study targeted all internal migrants in the country, not just those in Guatemala City. The target sample was 1,856 (78%) of former study participants living in Guatemala. This study reported a coverage of 85% (n=1,571), excluding those that had died (n=272), were untraceable (n=102), or had left the country (n=163).

### 3.2.3 Follow-up Study 2017-2019

The objective of this study was to explore the contributions of early-life circumstances and child cognitive potential to the development of adult social and human capital. The target sample was 1,643 (69%) participants who were presumed alive and living in Guatemala and were eligible for enrollment. The coverage of this study was 77% (n=1,268), excluding those participants that had died (n=385), were untraceable (n=109), or migrated abroad (n=255). By 2017, participants were 40-57 years of age. Measures collected in eligible cohort participants included cognitive ability and socioemotional functioning.

#### *3.2.3.1 Cognitive measures*

Non-verbal fluid intelligence was measured using the Raven's Progressive Matrices Test (10). Most study subjects were administered the test in 2015 (for a different study), but additional tests were administered in 2017, for those who did not participate in 2015. The Raven's Progressive Matrices test consists of a pattern for which there is a missing piece. Participants were asked to select the missing piece, from 8 possible options, to complete the pattern. Three of the five scales (A, B and C, with 12 questions each, for a maximum possible score of 36) were administered since previous applications in this population show that few participants were able to progress beyond the third scale. The proportion of correct responses served as the primary measure.

Three core executive functions (i.e., working memory, inhibitory control and cognitive flexibility) were measured using three tests of NIH Toolbox, all translated and validated into

Spanish and administered using tablet devices (11, 12). Inhibitory Control was evaluated with the computerized version of NIH Toolbox Flanker Inhibitory Control and Attention Test (12). The task requires participants to indicate the left-right orientation of a centrally presented stimulus while inhibiting attention to the potentially incongruent stimuli that surround it (i.e., the flankers, typically two on either side). On some trials, the orientation of the flanking stimuli is congruent with the orientation of the central stimulus, and on others it is incongruent. Both accuracy and reaction time were recorded. We used the NIH toolbox computed scores which uses a two-vector algorithm which integrates accuracy and reaction time scores.

Cognitive flexibility was measured by NIH Dimensional Change Card Sort (DCCS) Test. In this task individuals are shown two figures (e.g., a blue rabbit and a red boat) and are asked to sort a series of bivalent test cards (e.g., red rabbits and blue boats) first according to one dimension (e.g., color), and then according to the other (e.g., shape) (12). The same NIH toolbox computed scores, which uses a two-vector algorithm which integrates accuracy and reaction time were used.

Working memory was assessed with the computerized Spanish-language version of the NIH Toolbox List Sorting Working Memory test (13). The task requires participants to sort and sequence information that is visually and auditorily presented to them with illustrated pictures (animal or a piece of food or both). Participants were required to verbally sequence the information. The total number of correct responses for a maximum score of 26 was recorded and used as the primary measure.

Preliminary findings examining the validity and reliability of the NIH Toolbox tests in the Guatemalan population showed good test-retest reliability with intraclass correlation coefficients of 0.76 for Flanker, 0.80 for DCCS and 0.71 for list sorting tests (14).

*3.2.3.2 Socioemotional measures*

Socioemotional functioning was assessed using standardized scales for subjective happiness, life satisfaction, meaning and purpose, self-efficacy, emotional support, spirituality and religion, and mental health. To assess happiness the Lyubomirsky scale of global subjective happiness was used (15). Participants were asked to rate 4 items on a 5-point Likert scale ranging from 1 (Very unhappy) or (Not at all) to 5 (Very happy) or (A great deal). Item 4 “Some people are generally not very happy. Although they are not depressed, they never seem as happy as they might be. To what extent does this characterization describe you?” is reverse coded such that higher values represent higher happiness.

Life satisfaction is a component of subjective well-being that reflects the cognitive evaluation of whether one is happy with one’s life. General life satisfaction was measured by the NIH Toolbox General Life Satisfaction Survey (16). It consists of 5 items assessing global feelings and attitudes about one's life. Participants rated these items on a 5-point Likert scale ranging from 1 (*Strongly Disagree*) to 5 (*Strongly Agree*). Item 3 “I wish I had a different kind of life” was reverse coded such that higher values represent higher life satisfaction.

Meaning and purpose are conceptualized as having goals, a sense of direction, and a feeling that there is meaning to life (17). It is characterized by the extent to which people feel their life matters or makes sense. Participants rated 9 items of the NIH Toolbox Meaning and Purpose Survey on a 5-point Likert scale ranging from 1 (Strongly disagree) to 5 Strongly agree) (16). Items 5 “My life has no clear purpose” and 9 “there is not enough purpose in my life” were reverse coded such that higher values represented higher meaning and purpose.

Self-efficacy is described as a person's belief in his/her capacity to manage, function and have control over meaningful events. Respondents' sense of global self-efficacy was assessed using the NIH Toolbox Self-Efficacy Survey (18). Participants rated 10 items on a 5-point Likert scale ranging from 1 (Never) to 5 (Very often).

In all scales, computed scores were created as the sum of all items. For scales with missing items, a two-way imputation approach was applied (19). Other measures included in chapter 6 of this dissertation are emotional support, spirituality and religion and mental health.

To assess emotional support the fixed 8 item form of the NIH Toolbox Emotional Support Survey was used (20). Each item administered had a 5-point Likert scale with options ranging from 1 “Never” to 5 “Always.”

Spirituality and religion was assessed using the hope and faith facets of the World Health Organization Quality of Life Spirituality, Religiousness and Personal Beliefs WHOQOL-SRPB questionnaire (21). Each facet includes 4-items on a 5-point Likert scale. Computed scores were calculated as the sum of all items for each facet.

The WHO Self-Reporting Questionnaire (SRQ-20) was used to assess mental health. The SRQ-20 is a screening tool for mental disorders specifically designed for developing countries, consisting of 20 yes/no questions that add up to a maximum total score of 20 (22). Higher values are indicative of worse symptomology.

## 3.3 Training and Data Collection

Field workers were trained and standardized in the correct administration of the NIH toolbox modules and other survey instruments. Training was conducted over three weeks in Guatemala City, and repeat training and quality control were undertaken routinely every six months. Before the commencement of the study, instruments were reviewed, and pilot tested for cultural appropriateness in three villages that shared similar demographic and economic characteristics with those from the study. The pilot study indicated the need to replace test items in the NIH toolbox, as part of the list sorting task. *Pumpkin* was substituted with *papaya*, *cherry* with *níspero* (loquat) and *blueberry* with *nance* (small round tropical fruit) (14).

Enumerators visited each participant's home to explain the procedures and time required for administering the tests and questionnaires. If the person agreed, the enumerator gave an appointment to the research facility that was established in a rented building in the study village. Residents of Guatemala City and surrounding areas (~25% of the study sample) were invited to attend INCAP headquarters to be interviewed there. For participants who lived elsewhere in Guatemala, appointments were made by phone, and respondents were invited to Guatemala City for the interview. All transportation costs and overnight accommodation if needed were reimbursed.

### 3.3.1 Study Approval

Ethical approval for the study procedures was obtained by the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City-Guatemala and the Institutional

Review Boards of Emory University in Atlanta-GA. Written assent to participate in the study was obtained at each study wave.

## 3.4 Data Analysis

Structural Equation Modeling (SEM) techniques and its longitudinal applications (Growth Mixture Modelling) were used to examine associations between early-life environments and post-natal linear growth on cognitive and socioemotional outcomes in adulthood (chapters 4 and 5) as well as to explore cross-sectional interrelationships between cognitive and socioemotional domains (chapter 6).

### 3.4.1 Structural Equation Modeling

Because outcomes of interest for this dissertation could not be measured directly, appropriate analytical techniques for latent variables were needed. SEM is a powerful statistical technique that combines the capabilities from factor analysis, multiple regression, and path analysis yielding a unified general framework (23). SEM capabilities include modeling multiple dependent variables simultaneously, test overall model fit, decompose relationships into direct and indirect effects, and handle difficult data such as repeated measures over time with auto correlated errors and non-normal, categorical/ordinal outcomes (24). SEM uses a combination of indicators (single variables) and latent variables (underlying factors) and models the relations between variables' variances and covariances instead of individual data points. Thus, a large number of observed indicator variables can be reduced to latent variables. The focus is on the estimation of relations among latent variables, free of the influence of measurement error. This is made possible by integrating a measurement model that links observed variables to unobserved latent variables through confirmatory factor analysis (CFA), and a structural model that links the latent variables to each other via a system of simultaneous equations into one unified model (23).

For model identification, at least three indicators are needed in a single factor. In this dissertation there was a sufficient number of indicators for all measures to estimate latent variables for outcomes of interest.

In application of CFA, the interest was in evaluating the extent to which a set of indicators/items in a particular instrument actually measured the latent variables/factors they were designed to measure. In other words, the factorial structure of the study instruments was confirmed.

As a first step, the degree to which the observed indicators loaded on their respective latent factors was examined. If the hypothesized CFA model fit the data well, the factorial structure was confirmed to be valid for the study population (see chapters 4 and 6). In a second phase, the structural relations between observed variables (i.e., exposure to nutritional supplementation) and latent factors was assessed (see chapter 4).

The Weighted Least Square Mean and Variance (WLSMV) estimation technique was used for ordinal/categorical variables (25). This estimator uses pairwise deletion of missing values.

Model fit was assessed using three commonly reported indices. The comparative fit index (CFI) (26), CFI > 0.90 for acceptable fit; Tucker-Lewis index (TLI) (27), TLI > 0.95 for good fit; and root mean square error of approximation (RMSEA) (28), RMSEA <0.08 for acceptable fit and <0.05 for good fit. Another common statistic is the $\chi^2$, which is very sensitive to sample size.

If model fit statistics were not acceptable, modification indices were examined to decide if covariance's should be included to improve model fit, and the model was re-specified (modification indices were only used in chapter 4).

Model estimation procedures in SEM involve minimizing the residuals (differences) between the sample variances/covariances and the variances/covariances estimated from the model. The basic hypothesis in SEM is given by:

*(1)* $\Sigma = \Sigma(\theta)$

Where $\Sigma$ denotes the population covariance matrix of observed variables *y* and *x* and can be expressed as a function of free parameters $\theta$ in a hypothesized model. The purpose of SEM model estimation is to find a set of model parameters $\theta$ to produce $\Sigma(\theta)$ so that $[\Sigma - \Sigma(\theta)]$ can be minimized. Differences between the model estimated variance/covariance and the sample variance/covariance matrix indicate how well the model fits the data.

A more detailed description of SEM model evaluation and modification is provided as follows:

*3.4.1.1 SEM Model Evaluation*

A unique feature of SEM is that it allows for overall model fit test. The purpose is to assess the extent to which the model estimated variance/covariance matrix differs from the observed sample variance/covariance matrix. If the difference between the observed and the model estimated variance/covariance matrices is not statistically significant, then the model fits the data well, supporting the plausibility of hypothesized relationships among variables (24). Evaluation of model fit should be conducted prior interpretation of parameter estimates. Various model fit indices have been developed. The most commonly used fit indices include the model $X_2$ statistic, Comparative fit index (CFI), Tucker-Lewis Index (TLI) and Root mean square error of approximation (RMSEA) (26-28).

The model $X_2$ statistic determines the magnitude of the divergence of the observed sample and the model estimated variance/covariance matrices. The expectation is for the test not to reject the null hypothesis (Ho: the residual matrix is cero), thus a non-significant $X_2$ is desired. Because $X_2$ is defined by N-1 times the fitting function, this test statistic is extremely sensitive to sample size. The larger the sample size, the more likely to reject the null hypothesis, thus the problem of type 1 error (rejecting the correct hypothesis) could arise.

Comparative fit index (CFI) compares the specified model with the null model (which assumes cero covariance's among the observed variables). CFI is defined as the ratio of improvement moving from the null to the specified model with values ranging from 0 to 1. Values closer to 1 indicate better model fit. Recommended cut-off values are CFI>0.90 for a good fit. Because CFI depends on the average size of correlations in the data, CFI values will not be high if the sample average correlations in the data are not high (26).

Tucker-Lewis Index (TLI) compares the misfit of a specified model to the misfit of the null model. TLI is an incremental fit index, where values range from 0 to 1. Values <0.90 indicate a need to re-specify the model. In complex models TLI values tend to be smaller because the more free parameters in a model, the fewer degrees of freedom specified, which can lead to smaller TLI values (27).

Root mean square error of approximation (RMSEA) measures the average lack of fit per degree of freedom. Values of 0 indicate a perfect fit. The suggested cut-off point for a good model fit is $\leq 0.06$ (28).

### *3.4.1.2 SEM Model Modification*

Modifications indices (MI) are used as a diagnostic tool to capture model misspecification. MI are associated with the fixed parameters of the model and indicate how much the model fit will be improved (through a decrease in $X_2$) if a particular model parameter is freed from a constraint in a subsequent model. The recommendation is for parameters with high MI values to be freed one at a time, from the largest to the smallest. However, parameters should not be added or removed only for model fit improvement, these must be justified theoretically (24).

### 3.4.2 Growth Mixture Modeling

A longitudinal application of SEM is Growth mixture modeling (GMM). GMM allows to identify unknown homogeneous classes or groups of individuals based on observed measures of interest, describe latent trajectories (longitudinal change of each unobserved sub-group), and examine differences in change among classes. Moreover, GMM allows assessing the effects of covariates on group or class membership and examine associations between class membership and other outcomes of interest over time.

Different methods are available to identify latent trajectories, these include latent class analysis (LCA), latent class growth analysis (LCGA), and latent class growth mixture modeling (LCGMM) (29). The assumption behind these methods is that different subgroups of individuals with comparable developmental trajectories are present in the data, thus the objective is to capture the population heterogeneity with a latent variable indicating the number of subgroups or classes using observed growth parameters (intercept and slope).

Differences between these methods are given by the assumptions regarding the individual trajectories within a certain class. In LCGA classes differ in trajectory shape, but within each class the individuals are assumed to have a similar growth trajectory (there is no within-class variation). In LCGMM, within each class individuals are allowed to differ in growth trajectory (so there can be within-class variation). However, a common limitation of LCGMM is that it is computationally more demanding leading to model non-convergence (29).

LCGA was used in chapter 5 of this dissertation as it can incorporate a variety of nonlinear forms allowing different distributions. For model stability, LCGA requires at least three data points per subject but can handle variability in the number of data points and their spacing.

Different test statistics were used to determine the optimal number of latent classes. These include Bayesian Information Criterion (BIC), entropy, the Lo-Medell-Rubin-Likelihood Ratio Test (LMR-LRT), Bootstrap Likelihood Ratio Test (BLRT) and posterior probability. The solution that best fitted the data was the one with the lowest BIC value, highest entropy, significant LMR-LRT, and BLRT p-value, and the highest posterior probability (>0.70 for each class). The interpretability of classes and the number of subjects in each class were taken into consideration. It is recommended that no less than 5% of subjects fall under each class.

### 3.5 Summary

The study population for this study consists of a follow-up assessment of the Institute of Nutrition of Central America and Panama (INCAP) Nutrition Supplementation Trial conducted between 1969-77 in four rural communities in eastern Guatemala. Data were collected longitudinally in pregnant and lactating women and 2,392 children between 0-84 months of age from 1969-77. There have been several waves of fieldwork since the original intervention study ended in 1977. For the present study, anthropometric, maternal and socioeconomic characteristics collected during the supplementation trial (1969-77), as well as cognitive measures collected in 2002-04, and 2015-17 follow-up waves were used. Most outcome measures were obtained in the last wave of fieldwork conducted between 2017-19. These include tests of non-verbal fluid intelligence, executive function, and socioemotional functioning.

The target sample for 2017 follow up was 1,643 participants who were presumed alive and living in Guatemala and were eligible for enrollment. Of them, 261 declined to participate, and 114 were not contacted after multiple attempts, and 1,268 provided informed consent.

Structural Equation Modeling (SEM) techniques and its longitudinal applications such as Latent Class Growth Analysis (LCGA) were used to address the study aims. SEM is a powerful statistical method that combines the capabilities from factor analysis, multiple regression, and path analysis into a unified framework. It uses a combination of observed indicators and latent variables and models the relations between variables' variances and covariances instead of individual data points. The focus of SEM is to model the associations among latent variables, free of the influence of measurement error. This is made possible because latent variables extract the common variance from multiple measures so that the unique variance and measurement error are largely eliminated.

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**CHAPTER 4:** Early-childhood nutritional supplementation and psychosocial stimulation influences on cognition and socioemotional functioning in growth-stunted Guatemalan adults.

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## 4.1 Abstract

**Background:** The extent to which early-life nutritional supplementation may produce long-term benefits on executive function and socio-emotional functioning has not been fully explored.

**Methods:** The objective of the present study is twofold. First, we use information from participants of the INCAP Longitudinal trial with available data collected between 1969-77 and new data collected between 2017-19 to examine associations between exposure to nutritional supplementation in the first 1,000 days and adult executive function and socioemotional capacities using regression models with double-difference (DD) estimates. Second, using additional data collected in this population between 1969-77 and 2002-2004, we use Structural Equation Modeling to examine associations between early childhood nutritional supplementation and psychosocial stimulation on cognitive ability at ages 26-42 years and executive function and socioemotional capacities at ages 40-57 years.

**Results:** DD-estimates showed positive associations between exposure to atole in the first 1,000 days and working memory (β=1.24 95% CI: 0.05, 2.42), cognitive flexibility (β=0.93 95% CI: 0.19, 1.68), latent EF (β=0.96 95% CI: 0.12, 1.79), meaning and purpose (β=1.51 95% CI: 0.33, 2.96) and self-efficacy (β=2.90 95% CI: 0.25, 5.55). SEM results showed positive direct and total associations between exposure to atole in the first 1,000 days and adult socioemotional functioning (Standardized (STD) β=0.44 95% CI: -0.02, 0.89 and STD β=0.47 95% CI: -0.13, 1.07, respectively), and cognitive ability (total association: STD β=0.34 95% CI: -0.12, 0.80). Positive associations were observed between psychosocial stimulation and executive function (STD β=0.46, 95% CI: 0.20, 0.72), and between psychosocial stimulation and cognitive ability (STD β=0.57, 95% CI: 0.28, 0.85).

**Conclusion:** Exposure to enhanced nutrition in the first 1,000 days had significant benefits on adult cognitive and socioemotional outcomes. Associations between psychosocial stimulation and cognitive abilities were stronger than those between nutritional supplementation and cognitive abilities. Early-life investments in nutrition and psychosocial stimulation may produce greater long-term benefits than nutritional supplementation alone.

**Keywords:** first 1,000 days, child development, nutrition, psychosocial stimulation

## 4.2 Introduction

The period from conception to age 2 years, known as “the first 1,000 days," is critical for growth and development of motor, cognitive, and socioemotional skills throughout childhood and adulthood (1, 2). Adequate experiences and environments during this sensitive period are crucial for optimal brain and child development. These include prenatal and postnatal nutrition, psychosocial stimulation, characteristics of the physical environment and maternal mental health.

Observational studies consistently show that nutritional deficits in the first 1,000 days result in impaired growth and cognitive development with long-lasting effects in social and human capital attainment (3). Furthermore, randomized trials of food supplements provided during critical age periods to undernourished children living in poverty suggest causal links between child undernutrition, motor and mental development (4-6), and later cognitive abilities (7, 8). Although associations between child undernutrition and cognitive abilities are well documented, the socioemotional consequences of early-life nutritional deficits are less well understood.

The development of socioemotional skills occurs along with sensory-motor, cognitive, and language capacities and provides the basis for emotional wellbeing and adult socioemotional functioning and behavior (9). Longitudinal studies examining associations between early-life nutritional status and later socioemotional outcomes show that children who were stunted or underweight in early-childhood show poorer social skills and attention, and more problems with conduct at school age than children of adequate nutritional status (10-12).

Only a few nutritional supplementation trials have examined long-term effects on socioemotional outcomes with follow-up periods limited through age 8 years (10, 13, 14).

Two of these studies were conducted in a subsample of school-age children who in early childhood participated in a community-randomized food supplementation trial in eastern Guatemala. Children were followed up at ages 6 to 8 years and examined in free-play peer interactions, including problem-solving activities, competitive games, and impulse-control situations. Results indicated that study participants who received higher levels of nutritional supplementation prenatally (through maternal supplementation during pregnancy), and from birth to age 2 years, showed more social involvement, interest in the environment, and were capable of showing more positive affective expression. Furthermore, these children were rated as more energetic and self-confident and were less frequently timid or anxious than children who received less supplementation (13, 14).

The objective of the present study is twofold. First, we use information from participants of the INCAP Longitudinal trial with available data collected between 1969-1977 and new data collected between 2017-2019 to examine associations between exposure to nutritional supplementation in the first 1,000 days and adult executive function and socioemotional capacities. Second, using additional data collected in this population between 1969-1977 and 2002-2004, we use Structural Equation Modeling (SEM) to examine associations between early-life psychosocial stimulation on cognitive ability at ages 26 to 42 years, and executive and socioemotional functioning at ages 40-57 years.

## 4.3 Background

### 4.3.1 INCAP Longitudinal trial

In the late 1960s, it was hypothesized that protein deficiency could affect learning through the inhibition of brain growth and myelination during critical periods of development. To test this hypothesis, a community-randomized food supplementation trial was conducted between 1969-1977 in four rural communities in eastern Guatemala. Two-pairs of villages matched by population size were chosen from a pool of 300 communities. Matched villages had similar health indicators and comparable socioeconomic characteristics. At the time of the study design, malnutrition and infectious diseases were endemic in all villages, average family incomes were very low (< $300 US per year), and most adults were illiterate (15).

One village from each pair was randomly selected to receive a nutritious supplement *"atole,"* and the other two villages received a control drink called *"fresco"* (16). *Atole* was a gruel type drink that contained 11.5 g of protein and 163 kcal per 180 ml. The control drink *"fresco"* was a refreshing low-energy drink that contained no protein. Both drinks contained equal concentrations of micronutrients. Each supplement was provided to all residents of the village in a supplementation center twice a day, in mid-morning and mid-afternoon. Attendance was open to all residents but recorded only in pregnant and breastfeeding women and children up to age 7 years (16, 17). The final sample consisted of 2,392 individuals born 1962-1977.

Between 2002-2004 and 2017-2019, individuals who participated in the nutritional trial in early childhood were re-surveyed. The aim in both follow-up assessments was to examine the contributions of early-life nutrition and other circumstances on adult social and human capital attainment.

4.3.2 Hypotheses for Pathways of Interest

The theoretical basis for our analytical approach derives from models of nutrition and social behavior and studies suggesting that early-life nutritional deficits compromise the child's ability to engage with the environment and respond to stimulation, leading to less responsive interactions with caregivers (18-21). Additionally, it has been proposed that undernourished children are often more irritable and withdrawn, causing caregivers to treat them with less sensitivity, resulting in altered patterns of brain development (22). We further enrich our conceptual framework with evidence from cognitive development studies indicating that executive function is crucial for socioemotional functioning and all forms of cognitive performance (23). Executive function, often considered a domain of cognitive function, is a broad term used to describe a set of higher-order cognitive processes that regulate various cognitive functions, including thoughts and behaviors for the attainment of goals (24).

**Figure 4.1** outlines our pathways of interest. We hypothesize that children who were exposed to atole in the first 1,000 days were less irritable, withdrawn, and more engaged with the environment. As a result, these children demanded and received more psychosocial stimulation from caregivers ($\beta_{21}$). Previous studies in this population have documented positive associations between early-life exposure to atole and higher scores in reading comprehension and IQ tests at ages 26-42 y ($\beta_{41}$) (8). In this study, we examine whether exposure to atole in the first 1,000 days is positively associated with executive function ($\beta_{31}$) and adult socioemotional functioning ($\beta_{51}$)

at ages 40-57 y. Studies conducted among institutionalized children have documented associations between early-life psychosocial deprivation and deficits in executive function ($\beta_{32}$) (25, 26). Pathways $\beta_{42}$ and $\beta_{52}$ are supported by evidence from studies in Jamaica documenting that a psychosocial stimulation intervention provided to undernourished children up to age 2 y resulted in higher cognitive performance at age 6 y (27), and fewer symptoms of depression, social inhibition, and reductions in violent behavior at age 22 y (28). Pathways ($\beta_{53}$-$\beta_{54}$) are supported by longitudinal studies showing that cognitive abilities influence various aspects of socioemotional functioning (24, 29).

## 4.4 Methods

### 4.4.1 Study population

Data for this analysis come from participants of the INCAP Longitudinal trial with data collected between 1969-1977, 2002-2004, and 2017-2019. Detailed information on coverage and attrition by 2002 is provided elsewhere (30). By 2017, of the original sample of 2392 participants, 385 had died, 255 had migrated abroad, and 109 were untraceable, resulting in 1643 who were presumed alive and living in Guatemala and were eligible for enrollment. Of these, 1268 provided informed consent (**Supplemental Figure 4.1**).

Ethical approval for the study procedures was obtained by the Institutional Review Boards of Emory University in Atlanta-GA, and the Institute of Nutrition of Central America and

Panama (INCAP) in Guatemala City-Guatemala. Written participant consent to participate in the study was obtained at each study wave.

### 4.4.2 Early-life Measures (1969-1977)

#### *4.4.2.1 Exposure to nutritional supplementation*

When the trial was launched in 1969, all children up to age 7 y, and those born between 1969-1977 were recruited and followed-up until they reached age 7 y or until the trial ended. Thus, the age and periods at which children were exposed to the intervention varied across participants. Our primary interest was to capture exposure to nutritional supplementation in the first 1,000 d. That is, exposed from conception through maternal supplementation during pregnancy and lactation, and from the child's own consumption before age 2 y. We characterized exposure to supplementation based on the child's date of birth and dates for which *atole* or *fresco* supplementation was offered in the villages. Supplementation was provided from January 1st or May 1st, 1969, in large and small villages, respectively, until February 28th, 1977, in all villages.

We created a dummy variable for exposure to nutritional supplementation using three levels: (1) fully exposed in the first 1,000 d, (2) partially exposed in the first 1,000 d, and (3) not exposed at all in the first 1,000 d. For sensitivity analysis, we also computed a 2-level exposure variable: (1) exposure to nutritional supplementation during the full first 1,000 d, and (2) partial and no exposure to nutritional supplementation during the first 1,000 d.

*4.4.2.2 Psychosocial Stimulation*

We retrieved archived data on social and intellectual stimulation received by participants in their home environments during early childhood. Data on home stimulation was assessed between 1974-1975, through direct observation of the number of toys, pictures, books, and other stimulating material objects in the child's home. It also included an interview with mothers assessing child-play practices and interaction with caregivers. A composite score of these measures was available for analysis.

An indicator denominated "task instruction" was selected by the psychologists in the project as a measure of the parents' efforts to provide adult modeling and purposeful learning opportunities. Data on task instruction were obtained from repeated annual interviews conducted between 1969-1975 and included assessments of the interaction of caregivers and siblings with the child in three activities: teaching the child how to count, how to do a household task, and accompanying the child to a nearby town. A composite score of repeated measures collected between 1969-1975 was available for analysis.

*4.4.2.3 Potentially Confounding Variables*

During the original trial, information on maternal characteristics, including completed grades of schooling, age at child's birth, and maternal height was obtained by interview. Maternal height was measured to 0.1 cm using standardized protocols.

Information on socioeconomic status was obtained from village census conducted in 1967 and 1975 of household characteristics and consumer durable goods measured in participant households. A single combined score was created using principal components analyses (31). The 1967 index score was used for participants born before January 1971, and the 1975 index score for those born from January 1971 onwards.

### 4.4.3 Adult Measures (2002-04)

A comprehensive assessment of educational attainment was obtained by interview, including the highest grade of formal and informal education completed. Tests of intelligence were assessed with the Raven's Progressive Matrices test (sets A, B, and C), a non-verbal assessment of cognitive ability (32). Additionally, all literate participants were administered the Interamerican Series test of Reading Comprehension and Vocabulary. We calculated scores as the sum of correct responses for each test.

### 4.4.4 Adult Measures (2017-19)

#### *4.4.4.1 Executive Function*

We assessed three core executive functions (working memory, inhibitory control, and cognitive flexibility) using computerized Spanish-version tests from the cognition battery of the NIH Toolbox. A complete description of these tests, including their validation, adaptation for Guatemala, and training for their administration, are provided elsewhere (33).

*Working memory* was assessed using the List Sorting Working Memory Test, consisting of a series of objects (i.e., animal or food items) that are visually and auditory presented on a screen one at a time. In a series of trials, participants were required to memorize and repeat the information presented to them. We computed a final score as the sum of total items correct across trials (34).

*Inhibitory control* was measured using the Flanker Inhibitory Control and Attention Test. The task requires participants to indicate the left-right direction of a centrally presented arrow while inhibiting attention to two flankers on either side that surrounds it. On congruent trials, the orientation of the flanking stimuli matches the orientation of the central stimulus, and on incongruent trials, they face the opposite direction (34).

*Cognitive flexibility* was measured with the Dimensional Change Card Sort (DCCS) test. Participants were presented with two figures and asked to sort them in a series of trials, first according to their color and then according to their shape (35). For both Flanker and DCCS tests, we used the NIH Toolbox cognition composite scores, which are based on a combination of accuracy and reaction time (36).

#### *4.4.4.2 Socioemotional Functioning*

We assessed *happiness* with the use of the Lyubomirsky Global Subjective Happiness scale (37). Responses were on a 5-point Likert scale ranging from 1 (very unhappy or not at all) to 5 (very happy or a great deal). Final scores were calculated as the mean of all items.

*Life satisfaction* was assessed with the NIH Toolbox General Life Satisfaction scale (38), consisting of 5-items assessing global feelings and attitudes about one's life. Responses were rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).

*Meaning and purpose* was measured with the NIH Toolbox Meaning and Purpose scale consisting of 9-items rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree) (38).

*Self-efficacy* was measured using the NIH Toolbox Self-efficacy scale. Participants rated 10-items on a 5-point Likert scale ranging from 1 (never) to 5 (very often) (39). We calculated the final scores for each scale as the sum of the item scores on that scale. For all socio-emotional scales with missing items (<1%), we applied a two-way imputation approach (40).

### 4.4.5 Inclusion and Exclusion

We restricted the analysis of the first aim to participants who had completed at least one survey instrument in 2017-2019 and provided adequate data to be analyzed (n=1,268). For the second aim we used all adequate and available information collected between 1969-1977, 2002-2004, and 2017-2019 (n=1,640).

### 4.4.6 Statistical Analysis

For the first aim we investigate associations between full and partial exposure to nutritional supplementation in the first 1,000 d on adult executive function and socioemotional capacities using linear regression models with double-difference (DD) estimators controlling for potentially confounding variables. The DD-estimator captures the differential effect of the intervention in children exposed to *atole* relative to *fresco* during critical windows of exposure. The first difference compares the average change in outcome across children exposed to *atole* in the first 1,000 d relative to *fresco*. The second difference subtracts the average change in outcome across village treatments outside the first 1,000 d window. The interaction term between treatment assignment and age of exposure to supplementation represents the differential effect of full or partial exposure to *atole* in the first 1,000 d (DD-estimator). Models included the DD-estimator, dummy variables of study villages to control for village fixed effects, a categorical variable for age of exposure to the intervention, birth year to control for the age range of the study sample, SES in 1969-1977, maternal grades of schooling, the logarithm of maternal age at child's birth and maternal height (8, 41). Because some children were siblings, we accounted for clustering at the household level, and we stratified our models by sex. We used multiple imputation (MI) techniques for missing values on covariates. The prevalence of missing information was 21.3% for maternal height, 3.5% for maternal grades of schooling, and 0.7% for maternal age at respondents' birth. We conducted most of the analyses in Stata 15 and we used Mplus 8 for models assessing latent executive function.

For the second aim, we use SEM to examine pathways between exposure to nutritional supplementation in the first 1,000 d and adult socioemotional functioning through psychosocial stimulation, cognitive ability and executive function. An SEM model is a two-part model consisting of confirmatory factor analysis or measurement model, followed by a structural model. The measurement model assesses factor loadings while the structural model examines associations between factors and observed variables.

The model included dummy variables of the interaction term between treatment assignment and age of exposure as the exogenous variable using 3-levels: (1) exposure to *atole* during the full first 1,000 days; (2) exposure to *atole* during a partial period of the first 1,000 days; and (3) no exposure to *atole* during the first 1,000 days as the reference category. We also conducted sensitivity analyses using a 2-level exposure variable: (1) exposure to *atole* during the full first 1,000 days; and (2) partial and no exposure to *atole* during the first 1,000 days as the reference category.

We modeled “home stimulation” and “task instruction” scores as the latent construct “psychosocial stimulation.” List Sorting Working Memory, Flanker Inhibitory Control and Attention, and DCCS Tests scores obtained in 2017-2019, were modeled as the latent construct “executive function." Scores on Reading comprehension, Vocabulary, and Raven's Progressive Matrices obtained in 2002-2003 were modeled as a latent construct: “cognitive ability." Individual Likert-item responses for Meaning and Purpose and Self-efficacy Scales obtained in 2017-2019, were modeled as latent sub-domains of “socioemotional functioning."

Additionally, in separate models, we tested the joint effects of exposure to *atole* during the full first 1,000 days and psychosocial stimulation on cognitive and socioemotional outcomes using interaction terms.

All paths in our models controlled for dummy variables for village fixed effects, SES in 1967-1975, sex, maternal grades of schooling, maternal age at respondents' birth and maternal height (log-transformed), a categorical variable for age of exposure to the intervention, birth year and confidence intervals accounted for clustering of subjects within family. We estimated standardized direct associations, total indirect associations, and total associations for each pathway.

We interpreted the adequacy of model fit with three commonly reported indices. The comparative fit index (CFI), the Tucker-Lewis index (TLI), and the Root Mean Square Error of approximation (RMSEA) (42-44). CFI > 0.90 for good fit; TLI > 0.95 for good fit; and RMSEA <0.08 for acceptable fit and <0.05 for good fit. If model fit was below the threshold for a good fit, we examined modification indices to improve model fit, and if proposed pathways or covariances between variables were justifiable, we re-specified the model.

All models were estimated using MPLUS 8 using the WLSMV estimator for categorical/ordinal responses (45), with pairwise deletion for missing values. Interactions between psychosocial stimulation latent variable and exposure to nutritional supplementation were estimated using the XWITH command in MPLUS 8.

**4.5 Results**

Descriptive statistics of the study population are presented in **Table 4.1.** In pooled models, partial exposure to *atole* during the first 1,000 days was positively associated with List Sorting working memory scores (β=1.24 95% CI, 0.05, 2.42), and EF latent construct (β=0.96 95% CI, 0.12, 1.79). Full exposure to *atole* in the first 1,000 days was associated with a 1.51-point increment in Meaning and Purpose scores (95% CI, 0.33, 2.69) in both women and men, and with a 2.90-point increment in Self-efficacy scores (95% CI, 0.25, 5.55) in women **(Table 4.2).**

**Figure 4.2** shows the measurement and structural mediation models for the association between partial or full exposure to nutritional supplementation in the first 1,000 days and adult socioemotional functioning through psychosocial stimulation, executive function, and cognitive ability. The model had good fit (RMSEA=0.02, CFI=0.99, TLI=0.98). We observed significant direct associations between psychosocial stimulation and executive function (Standardized (STD) β=0.46, $p<0.01$), and between psychosocial stimulation and cognitive ability (STD β=0.57, p<0.01). Furthermore, we found that executive function and cognitive ability were strongly inter-correlated (r=0.91, p<0.01).

**Table 4.3** shows standardized coefficients for direct associations, total indirect associations, and total associations for each predictor and dependent variable in our models using a 3-level exposure to nutritional supplementation. We found a significant total association between full exposure to *atole* in the first 1,000 days and adult socioemotional functioning (STD β=0.47 95% CI, -0.13, 1.08). Furthermore, we observed positive total associations between full and partial exposure to *atole* in the first 1,000 days on cognitive ability (STD β=0.34 95% CI, -0.12, 0.80; p=0.05 and STD β=0.34, 95% CI, -0.07, 0.74, p<0.05, respectively).

Results on the association between psychosocial stimulation and socioemotional functioning showed a significant total association (STD β=0.23 95% CI, -0.03, 0.50), and a significant total indirect association (STD β=0.13 95% CI, -0.01, 0.27) (Table 4.3).

**Supplemental Figure 4.2 and Supplemental Table 4.1** show results from sensitivity analysis using a two-level of exposure (full vs. partial and no exposure). Results remained similar to those obtained using a three-level of exposure and showed a significant direct association on the relationship between full exposure to *atole* in the first 1,000 days and adult socioemotional functioning (STD β=0.44 95% CI, -0.02, 0.89).

We observed no interaction between full exposure to atole in the first 1,000 days and psychosocial stimulation on executive function, cognitive ability, and socioemotional outcomes **(Supplemental Figures 4.3-4.5).**

## 4.6 Discussion

To our knowledge, our study is the first to examine the effect of an early-childhood nutrition intervention on adult executive function and socioemotional capacities. Our results indicate that exposure to enhanced nutrition during the full first 1,000 days had significant benefits on adult cognitive and socioemotional outcomes. Furthermore, our findings show no evidence that psychosocial stimulation, executive function, or cognitive ability mediate the association between nutritional supplementation in the first 1,000 days and adult socioemotional functioning; rather, our results show significant direct and total associations. These findings are consistent with two previous studies conducted in this cohort documenting better behavioral outcomes at ages 6-8 y among children that received higher intakes of nutritional supplementation during infancy (13, 14). Our results, together with those from Barrett et al. (1982), suggest that nutrition interventions have long-lasting effects on socioemotional capacities, and that benefits acquired in childhood remain throughout adulthood.

Furthermore, our results show a total effect of exposure to nutritional supplementation on adult cognitive ability (STD $\beta$=0.34, p=0.05). This finding is consistent with previous analysis documenting significant benefits of nutritional supplementation on adult reading comprehension and intelligence test scores (8). Our analysis confirms and extends previous findings by additionally accounting for measurement error.

Moreover, previous studies in this population have documented that the nutritional intervention increased completed grades of schooling among women (8). In our analysis, we did not control for schooling, nor we included schooling as a mediator variable. The former because schooling would act as a mediator and not a confounder, and the latter given our interest in cognitive rather than social mediators.

A compelling explanation for the observed associations between nutritional supplementation on cognitive and socioemotional outcomes could be attributed to the role of stress. It is well documented that during critical periods of brain development, prolonged exposure to stress hormones can impair the development of neural connections, particularly in regions of the brain dedicated to higher-order skills causing life-long problems in learning and behavior (46). It has been documented that undernutrition exposes the body to stress hormones, specifically cortisol (47, 48). Moreover, children living in poverty are usually more exposed to multiple stressors (e, g., domestic or community violence, poor social support, unresponsive parenting). Thus, we interpret our findings as evidence that early-life exposure to enhanced nutrition may have the potential to mitigate the disruptive effects of multiple stressors during critical windows of brain formation. The specific pathways through which this could operate remain to be understood.

Another important result was to find strong, positive, and direct associations between psychosocial stimulation and cognitive ability, executive function and socioemotional functioning. The total association between psychosocial stimulation and socioemotional functioning was smaller in magnitude than the one observed between exposure to supplementation and socioemotional outcomes (STD $\beta$=0.23 vs. STD $\beta$=0.47 respectively, $p<0.05$ in both). However, associations between psychosocial stimulation and cognitive abilities were stronger than those between nutritional supplementation and cognitive abilities.

The concern that children could be affected by parental exposure to the trial was raised during the design phase of the intervention. The active presence of the team members in the communities, together with home visits to monitor child growth had the potential to influence social stimulation. Furthermore, daily attendance at the supplementation center could have acted as a social outlet for infants and mothers (49). These concerns were resolved with the inclusion of a nutritional intervention, including a feeding center on control communities. However, the possibility that the intervention might have influenced social stimulation in both treatment and control communities cannot be ruled out. Our results indicated no interaction between exposure to atole in the first 1,000 days and psychosocial stimulation on cognitive and socioemotional outcomes, suggesting that the observed associations between psychosocial stimulation, cognitive and socioemotional outcomes acted independently from the nutritional intervention.

Our study had unexpected results. We found positive associations between nutritional supplementation and executive function among participants that were partially rather than fully exposed to *atole* in the first 1,000 days. The majority of children that were partially exposed to *atole* during this critical window of development were closer to reach age 2 years. This is relevant because although the neural connections that support the development of higher-order cognitive functions peak at 12 months of age, it is well established that the development of executive function skills extend well beyond the first 1,000 days window. For instance, studies show that the development of working memory capacity starts in the first year of life and continues at least into adolescence with alternating periods of rapid and more stable growth (24). The first spur is between the ages of 2 and 8 years (50-53). Thus, these findings suggest that the benefits of improved nutrition on the development of executive function skills extend the first 1,000 days-window and may be involved with pruning and myelination processes that occur later in their development. More research is needed to understand the role of timing on the association between improved nutrition and development of executive function skills.

There are limitations to this study. The main limitation is that additional and comparable measures of executive function and socioemotional capacities were not available at earlier points in time, for instance, during childhood or adolescence. However, this is unlikely to represent a major threat to the validity of our findings given the substantial stability of executive function skills reported throughout adolescence and early-adulthood (54-56). Another limitation is that psychosocial stimulation was not randomized, so baseline differences that were not fully captured by control variables in our models could be obscuring our results.

Our study also has strengths. A major strength of this dissertation was the use of rich and extensive longitudinal data collected over 50 years. In addition, the methods used for assessing the effects of nutritional supplementation on cognitive and socioemotional outcomes used an experimental design and were well suited for evaluating the intervention, allowing for causal inferences to be more plausible. The use of double difference estimators allowed to isolate the effect of exposure to *atole* in the first 1,000 days, relative to the control group *fresco* controlling for village-level differences or other period or cohort effects. This was relevant because treatment assignment was allocated at the village level, and with only two villages per treatment, potential baseline differences between treatment groups may not have been adequately addressed by randomization. Another analytical strength of this dissertation was the use of structural equation modeling techniques. Because latent variables extract the common variance from multiple measures, specific variance and measurement error are largely eliminated, resulting in increased statistical power and more accurate parameter estimates.

Taken together, our findings suggest that in populations in which undernutrition is prevalent, childhood interventions that include nutritional supplementation components may help mitigate the damaging effects of early-life adversity on socioemotional outcomes.

In addition, our data, together with findings from studies in Jamaica (27, 28) and Pakistan (57), suggest that early-life investments in nutrition and psychosocial stimulation, including caregiver-child interactions, may produce greater long-term benefits on cognitive functioning than nutritional supplementation alone. These findings are consistent with current understandings of child development research strongly advocating for the promotion of nurturing and responsive caregiving for children to reach their full developmental potential (58).

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**Table 4. 1** Descriptive statistics (Mean ± SD or %) of the study population by sex.

| | n | Women | n | Men |
|---|---|---|---|---|
| **1969-77 trial** | | | | |
| Maternal schooling (years) | 815 | 1.3 ±1.5 | 825 | 1.3 ±1.6 |
| Maternal age at the respondent's birth (years) | 815 | 27.2 ± 7.1 | 825 | 27.4 ± 7.1 |
| Maternal height (cm) | 815 | 148.6 ± 5.1 | 825 | 148.6 ± 4.9 |
| Socioeconomic status (%) | 815 | | 825 | |
| Low | | 37.5 | | 37.4 |
| Medium | | 31.8 | | 33.5 |
| High | | 30.7 | | 29.1 |
| Exposure to Atole in first 1,000 d (%) | 815 | | 825 | |
| Full exposure | | 22.0 | | 20.6 |
| Partial exposure | | 18.0 | | 17.9 |
| No exposure | | 59.9 | | 61.5 |
| Home stimulation score (std) | 654 | 0 ± 1.0 | 666 | 0 ± 1.0 |
| Task instruction score (std) | 729 | 0 ±1.0 | 747 | 0 ± 1.0 |
| **2002-04 follow-up** | | | | |
| Reading comprehension score (out of 40) | 509 | 23.4 ± 6.6 | 446 | 23.4 ± 6.4 |
| Vocabulary score (out of 45) | 509 | 18.3 ± 9.6 | 446 | 21.3 ± 10.1 |
| Raven Progressive Matrices score (out of 36) | 615 | 16.4 ± 5.4 | 529 | 19.5 ± 6.4 |
| **2017-19 follow-up** | | | | |
| Age (y) | 815 | 47.5 ± 4.3 | 825 | 47.4 ± 4.1 |
| Schooling (y) | 596 | 4.7 ± 3.5 | 518 | 5.5 ± 3.6 |
| List Sorting Working Memory score (out of 23) | 670 | 11.3 ± 3.8 | 541 | 12.7 ± 3.9 |
| Flanker NIH computed score | 671 | 5.4 ± 1.1 | 542 | 5.8 ± 1.2 |
| DCCS NIH computed score | 677 | 5.1 ± 1.9 | 546 | 5.4 ± 1.9 |
| Lyubomirsky Happiness score (out of 5) | 700 | 4.0 ± 1.0 | 553 | 4.1± 0.9 |
| Life Satisfaction score (out of 25) | 699 | 18.5 ± 3.5 | 553 | 18.9 ± 3.4 |
| Meaning and Purpose score (out of 45) | 698 | 36.2 ± 4.1 | 552 | 37.2 ± 4.1 |
| Self-efficacy score (out of 40) | 698 | 30.9 ± 7.1 | 552 | 31.4 ± 6.4 |

Abbreviations: DCCS Dimensional Change Card Sort; NIH National Institutes of Health

**Table 4. 2** Difference-in-difference estimates of full and partial exposure to nutritional supplementation in first 1,000 days on executive function and socioemotional outcomes by sex[1]

| | Full exposure to atole in first 1,000 d vs. no exposure | | | Partial exposure to atole in first 1,000 d vs. no exposure | | |
|---|---|---|---|---|---|---|
| | Pooled | Women | Men | Pooled | Women | Men |
| **Executive function (EF)** | | | | | | |
| List Sorting Working Memory score | 0.34 (-0.76, 1.44) | -0.26 (-1.63, 1.11) | 1.13 (-0.67, 2.93) | 1.24 (0.05, 2.42) * | 1.82 (0.33, 3.32) * | 0.62 (-1.24, 2.47) |
| Flanker NIH score | 0.07 (-0.23, 0.38) | 0.12 (-0.27, 0.52) | 0.07 (-0.44, 0.58) | 0.29 (-0.03, 0.61) | 0.21 (-0.17, 0.59) | 0.46 (-0.07, 0.99) |
| DCCS NIH score | 0.22 (-0.37, 0.80) | 0.43 (-0.32, 1.20) | -0.07 (-0.97,0.82) | 0.29 (-0.29, 0.87) | 0.93 (0.19, 1.68) * | -0.52 (-1.47, 0.43) |
| Latent EF | 0.37 (-0.61, 1.35) | - [1] | 0.22 (-1.18, 1.63) | 0.96 (0.12, 1.79) ** | - [1] | 0.18 (-0.02, 1.39) |
| **Socio-emotional functioning** | | | | | | |
| Lyubomirsky Happiness score | 0.26 (-0.03, 0.54) | 0.23 (-0.17, 0.64) | 0.35 (-0.02, 0.72) | 0.26 (-0.02, 0.54) | 0.29 (-0.12, 0.71) | 0.27 (-0.11, 0.66) |
| Life Satisfaction score | 0.20 (-0.75, 1.15) | 0.40 (-0.86, 1.67) | -0.06 (-1.55,1.43) | 0.20 (-0.77, 1.17) | 0.84 (-0.49, 2.17) | -0.66 (-2.20, 0.88) |
| Meaning and Purpose score | 1.51 (0.33, 2.69) * | 1.23 (-0.40, 2.85) | 1.91 (0.20, 3.61)* | 0.67 (-0.59, 1.94) | 0.56 (-1.14, 2.25) | 0.87 (-0.94, 2.69) |
| Self-efficacy score | 1.87 (-0.08, 3.82) | 2.90 (0.25, 5.55) * | 0.61 (-2.26, 3.46) | 0.76 (-1.21, 2.74) | 1.45 (-1.25, 4.15) | -0.05 (-2.98, 2.88) |

Sample sizes were 670 and 541 (List Sorting Working Memory), 671 and 542 (Flanker NIH score), 677 and 546 (DCCS NIH score), 688 and 556 (Executive function latent variable), 700 and 553 (Lyubomirsky Happiness), 699 and 553 (Life Satisfaction), 698 and 552 (Meaning and Purpose and Self-efficacy) for women and men, respectively.

Estimates are linear regression coefficients (95% CI) for the interaction term specifying full and partial exposure to atole (relative to fresco) in first 1000 d vs. no exposure controlling for age at intervention (partial and full exposure in first 1000 d vs. no exposure), fixed effects of birth village, birth year, household wealth index in 1969-77, maternal years of schooling, logarithm of maternal age and maternal height. Pooled models controlled for sex. For missing covariates, we used Multiple Imputation techniques. Confidence intervals account for clustering at the mother level. *p < 0.05. **p<0.01.

1. Models did not converge

**Table 4. 3** Standardized direct associations, total indirect associations, and total associations between full and partial exposure to atole in first 1,000 days and adult socioemotional functioning through psychosocial stimulation, executive function and cognitive ability, (n=1,640)[1]

| Dependent variables | Predictors [2] | Standardized Coefficients (95% CI) Direct associations | Total indirect associations | Total associations |
|---|---|---|---|---|
| Psychosocial stimulation | Full exposure to atole | 0.14 (-0.22, 0.50) | | |
| | Partial exposure to atole | 0.21 (-0.09, 0.51) | | |
| Executive function 40-57 y | Full exposure to atole | -0.11 (-0.62, 0.39) | 0.06 (-0.11, 0.23) | -0.05 (-0.55, 0.45) |
| | Partial exposure to atole | 0.10 (-0.33, 0.53) | 0.09 (-0.05, 0.25) | 0.19 (-0.23, 0.62) |
| | Psychosocial stimulation | 0.46 (0.20, 0.72) ** | | |
| Cognitive ability 26-42 y | Full exposure to atole | 0.26 (-0.22, 0.74) | 0.08 (-0.13, 0.29) | 0.34 (-0.12, 0.80) [3] |
| | Partial exposure to atole | 0.22 (-0.20, 0.63) | 0.12 (-0.07, 0.30) | 0.34 (-0.07, 0.74) * |
| | Psychosocial stimulation | 0.57(0.28, 0.85) ** | | |
| Socio-emotional functioning 40-57 y | Full exposure to atole | 0.43 (-0.22, 1.08) | 0.04 (-0.26, 0.35) | 0.47 (-0.13, 1.08) * |
| | Partial exposure to atole | -0.01 (-0.51, 0.49) | 0.08 (-0.06, 0.24) | 0.07 (-0.42, 0.57) |
| | Psychosocial stimulation | 0.10 (-0.20, 0.40) | 0.13 (-0.01, 0.27) * | 0.23 (-0.03, 0.50) * |
| | Executive function | 0.14 (-0.60, 0.89) | | |
| | Cognitive ability 26-42 y | 0.11 (-0.65, 0.88) | | |

[1] Model fit statistics: RMSEA=0.02, CFI=0.98, TLI=0.98. Models controlled for village fixed effects, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondent's birth and maternal height (log-transformed), age at intervention, birth year, and accounting for clustering of subjects within family. Estimates are standardized coefficients

controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (partial or full exposure vs. no exposure), birth year and accounting for clustering of subjects within family. * P<0.05, ** P<0.01.

[2] Coefficients for full or partial exposure to atole are interpreted as the change in *Y* in *Y* standard deviation units when *X* changes from 0 to 1 (STDY in Mplus 8).

[3] P=0.05

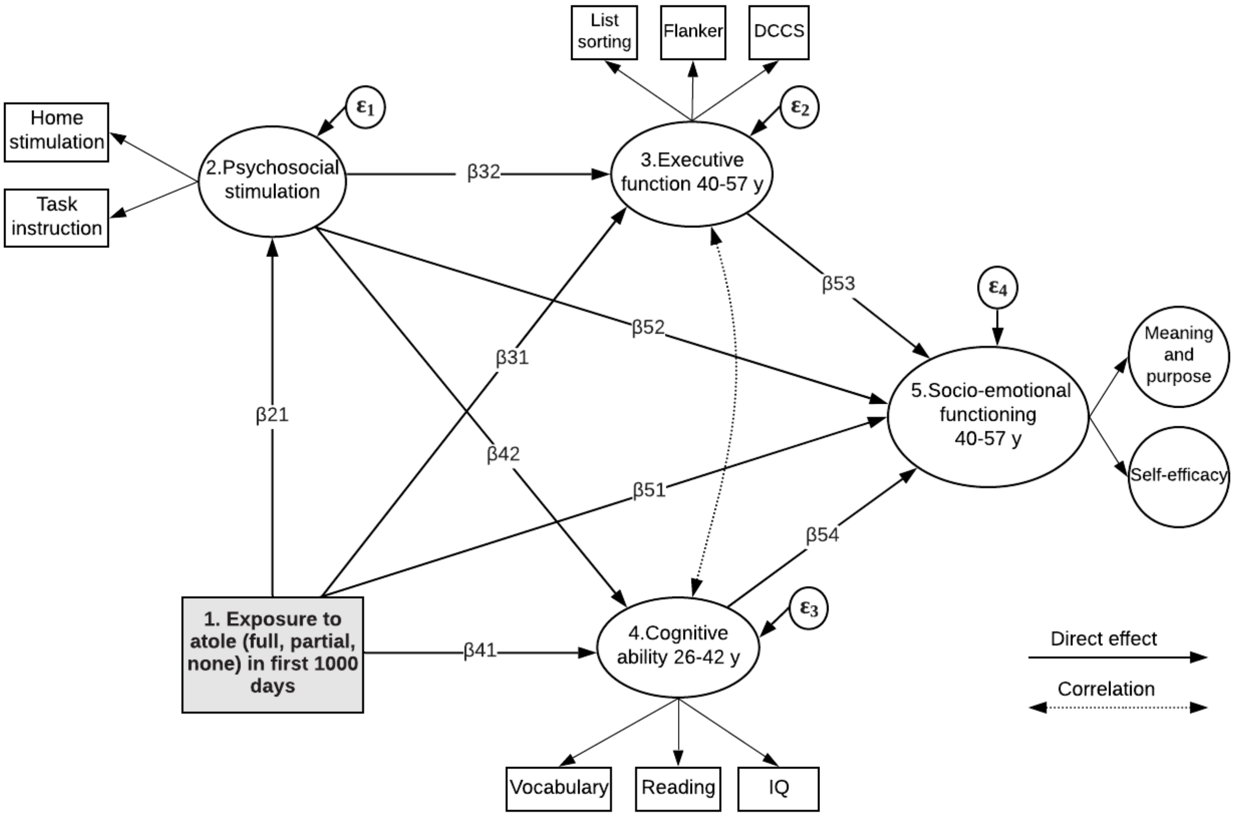



**Figure 4. 1** Hypothesized SEM model

Measures for domains 1 and 2 collected in early childhood, domains 3 and 5 collected at ages 40-57 y and domain 4 collected at ages 26-42 y. Abbreviations: DCCS Dimensional Change Card Sort.

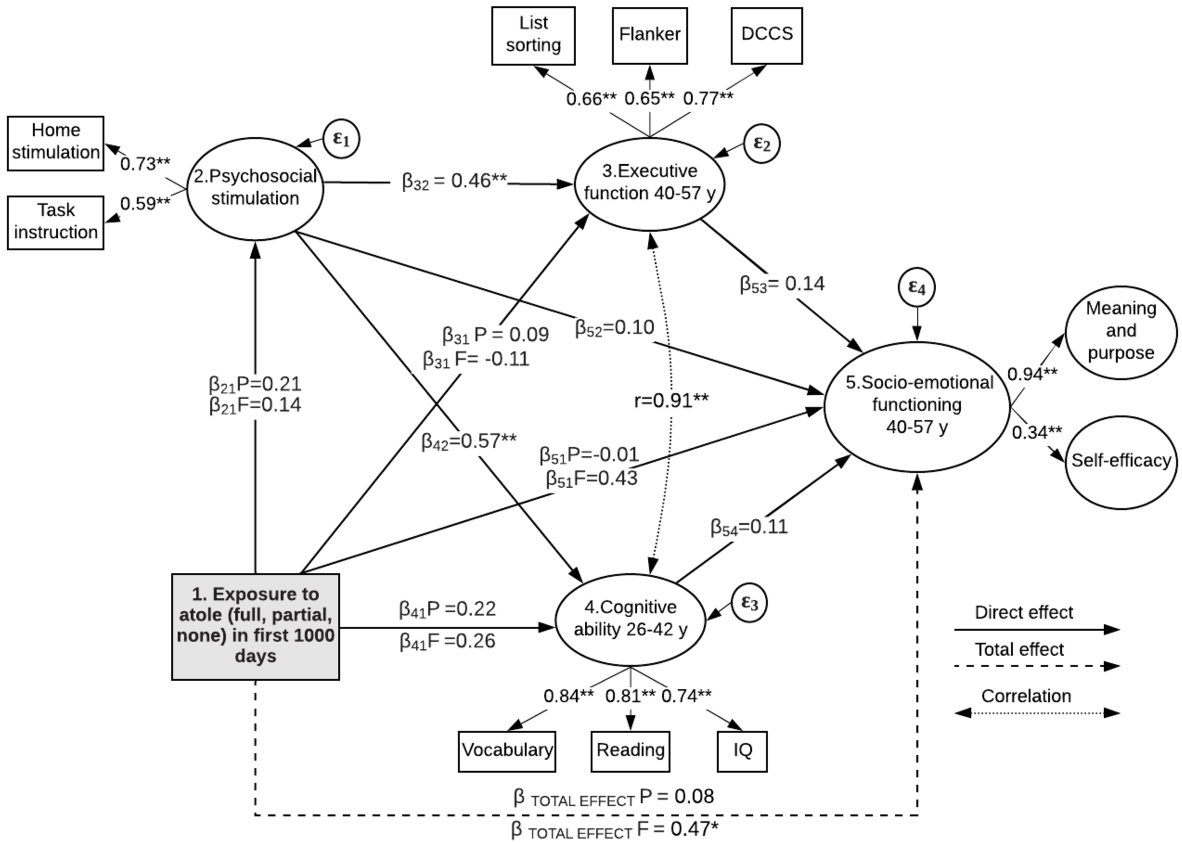



**Figure 4. 2** Fitted model of the association between exposure to atole in first 1,000 d and adult socioemotional functioning through psychosocial stimulation, executive function, and cognitive ability, (n=1,640)

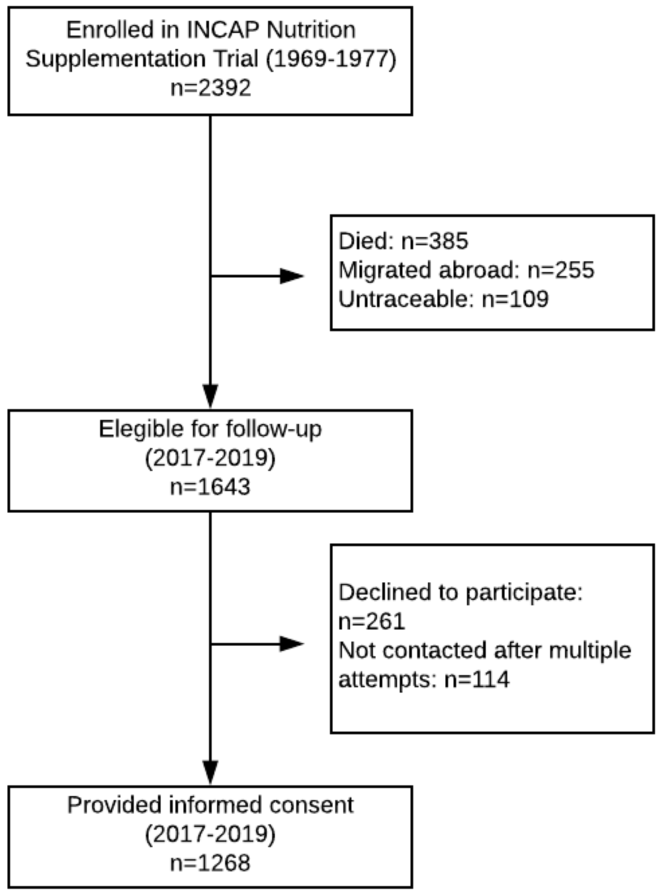
Model fit statistics: RMSEA=0.02, CFI=0.99, TLI=0.98. Estimates are standardized coefficients controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (partial or full exposure vs. none) and birth year and accounting for clustering of subjects within family. $\beta_{21}$, $\beta_{31}$, $\beta_{41}$, and $\beta_{51}$ are standardized coefficients (STDY in Mplus 8) for the interaction term specifying full and partial exposure to atole (relative to fresco*)* in first 1,000 d vs. no exposure interpreted as the change in *Y* in *Y* standard deviation units when *X* changes from 0 to 1. *p<0.05, **p<0.001.

**Supplemental Table 4. 1** Standardized direct associations, total indirect associations, and total associations between full exposure to atole in first 1,000 days (vs. partial and no exposure) and adult socioemotional functioning through psychosocial stimulation, executive function and cognitive ability (n=1,640) [1]

| **Dependent variables** | Standardized Coefficients (95% CI) | | | |
|---|---|---|---|---|
| | **Predictors** [2] | **Direct associations** | **Total indirect associations** | **Total associations** |
| Psychosocial stimulation | Full exposure to atole | 0.05 (-0.17, 0.27) | | |
| Executive function 40-57 y | Full exposure to atole | -0.16 (-0.52, 0.18) | 0.02 (-0.08, 0.13) | -0.14 (-0.49, 0.20) |
| | Psychosocial stimulation | 0.47 (0.20, 0.73) ** | | |
| Cognitive ability 26-42 y | Full exposure to atole | 0.10 (-0.25, 0.45) | 0.03 (-0.09, 0.16) | 0.13 (-0.20, 0.46) |
| | Psychosocial stimulation | 0.57 (0.28, 0.86) ** | | |
| Socio-emotional functioning 40-57 y | Full exposure to atole | 0.44 (-0.02, 0.89) * | 0.00 (-0.21, 0.22) | 0.44 (0.02, 0.86) ** |
| | Psychosocial stimulation | 0.10 (-0.21, 0.39) | 0.13 (-0.00, 0.28) * | 0.23 (-0.04, 0.49) * |
| | Executive function | 0.13 (-0.64, 0.90) | | |
| | Cognitive ability 26-42 y | 0.13 (-0.66, 0.92) | | |

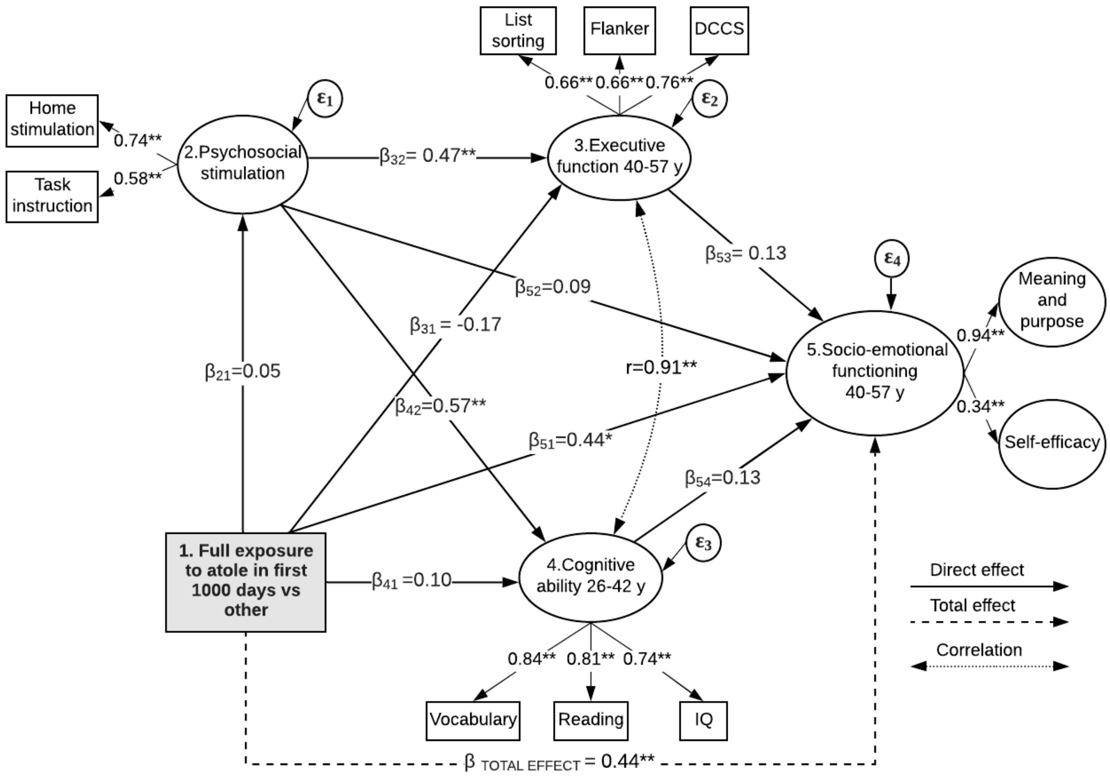
[1] Model fit statistics: RMSEA=0.02, CFI=0.98, TLI=0.98. Models controlled for village fixed effects, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondent's birth and maternal height (log-transformed), age at intervention, birth year, and accounting for clustering of subjects within family. Estimates are standardized coefficients controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (full exposure vs. partial and no exposure), birth year and accounting for clustering of subjects within family. * P<0.05, ** P<0.01.

[2] Coefficients for full exposure to atole are interpreted as the change in *Y* in *Y* standard deviation units when *X* changes from 0 to 1 (STDY in Mplus 8).



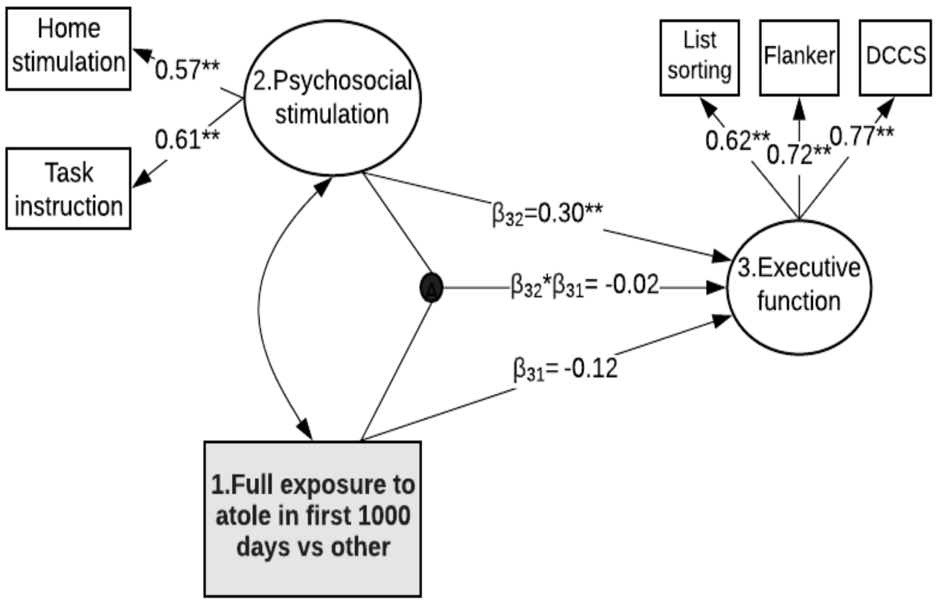

**Supplemental Figure 4. 1** Flowchart of study participants by 2017-19

By 2017, of the original sample of 2,392 participants, 385 had died, 255 had migrated abroad, and 109 were untraceable, resulting in 1,643 who were presumed alive and living in Guatemala and were eligible for enrollment. Of these, 1,268 provided informed consent.



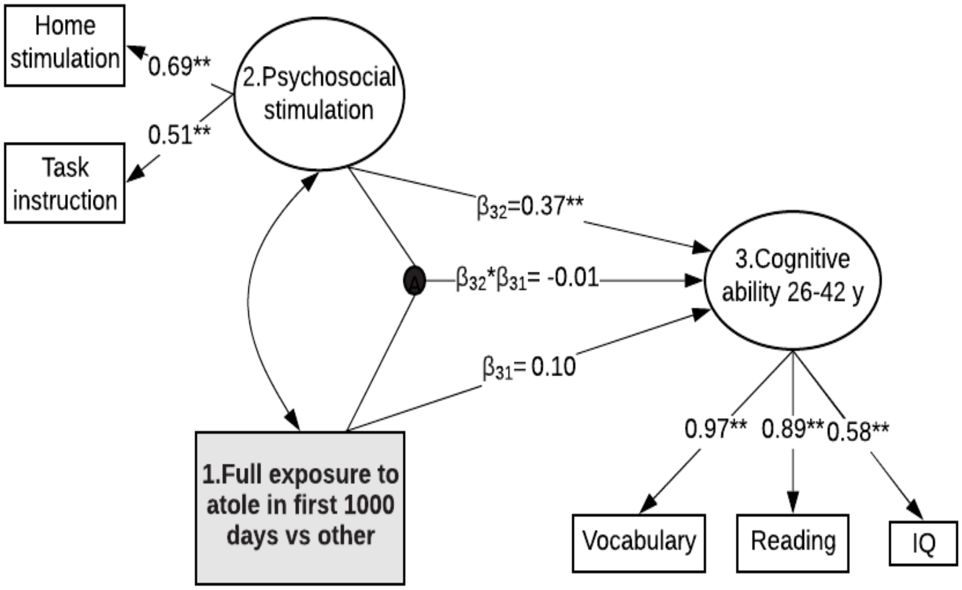

**Supplemental Figure 4. 2** Fitted model of the association between exposure to atole in first 1,000 d and adult socioemotional functioning through psychosocial stimulation, executive function, and cognitive ability (n=1,640)

Model fit statistics: RMSEA=0.017, CFI=0.98, TLI=0.98. Estimates are standardized coefficients controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (full exposure vs. other) and birth year and accounting for clustering of subjects within family. $\beta_{21}$, $\beta_{31}$, $\beta_{41}$, and $\beta_{51}$ are standardized coefficients (STDY in Mplus 8) for the interaction term specifying full exposure to atole in first 1,000 d (vs. other) interpreted as the change in *Y* in *Y* standard deviation units when *X* changes from 0 to 1. *p<0.05, **p<0.01.




**Supplemental Figure 4. 3** Model with interaction between full exposure to atole in the first 1,000 d and psychosocial stimulation on executive function, (n=1604)

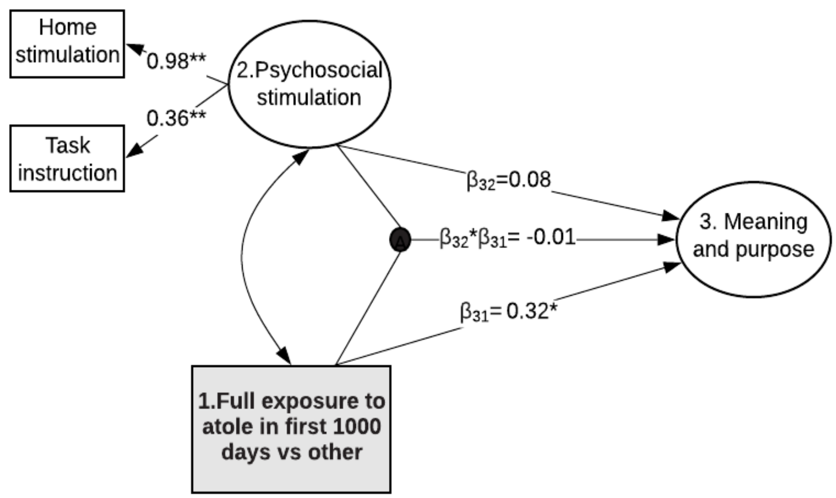
Estimates are standardized coefficients controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (full exposure vs. other) and birth year.



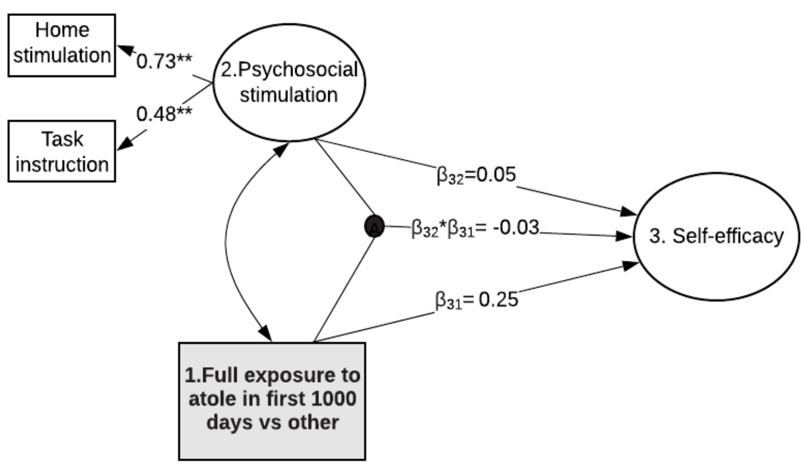

**Supplemental Figure 4. 4** Model with interaction between full exposure to atole in the first 1,000 d and psychosocial stimulation on cognitive ability, (n=1621)

Estimates are standardized coefficients controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (full exposure vs. other) and birth year.

A)




B)




**Supplemental Figure 4. 5** Models with interaction between full exposure to atole in the first 1,000 d and psychosocial stimulation on Meaning and Purpose (A), and Self-efficacy (B), (n=1604)

Estimates are standardized coefficients controlling for: dummy variables for three of the four villages of origin, socioeconomic status in 1967-75, sex, maternal years of schooling, maternal age at respondents' birth and maternal height (log-transformed), age at intervention (full exposure vs. other) and birth year.

**CHAPTER 5:** Associations between height-for-age linear growth trajectories from birth to 7 years and adult cognitive and socioemotional functioning in a Guatemalan cohort.

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## 5.1 Abstract

**Background:** Growth faltering in the first 1,000 d is associated with poor cognitive development and intellectual functioning, but less is known about predictors of linear growth trajectories and its associations with cognitive and socioemotional outcomes in adulthood.

**Objectives:** We aimed to: 1) examine the role of early-life characteristics on the pattern of height-for-age linear growth at ages 0 to 84 months; 2) Investigate associations between longitudinal trajectories of height-for-age linear growth on adult non-verbal fluid intelligence, executive function (working memory, inhibitory control and cognitive flexibility) and socioemotional functioning (happiness, life satisfaction, meaning and purpose and self-efficacy) at ages 40 to 57 years, and; 3) examine the mediating role of schooling on the association between height-for-age linear growth class membership and adult outcomes.

**Methods:** We prospectively followed 722 women and 777 men who had participated in a community-randomized food supplementation trial in early-childhood (1969-1977). We used Latent Class Growth Analysis to group children at ages 0 to 84 months, and a subset of them at ages 36 to 84 months, into sex-specific classes of common longitudinal trajectories of height-for-age z-scores (HAZ). We used multinomial logistic regression models to assess predictors of latent HAZ class membership and linear regression models to examine associations between latent HAZ growth trajectories at ages 0 to 84 months, and cognitive and socioemotional outcomes at ages 40 to 57 y.

**Results**: We identified 3 HAZ linear growth trajectories (high, medium and low) between 0 to 84 months in both genders. Arranging the trajectories from high to low, the estimated percentages were 34%, 50%, and 16%, among females, and 32%, 50%, and 18% among males.

Maternal height, socioeconomic status, and exposure to nutritional supplementation in the first 1,000 days were positively associated with membership to the high-HAZ linear growth trajectory. Linear regression models indicated a gradient of positive associations between HAZ trajectories and measures of cognitive ability and meaning and purpose at ages 40 to 57 y in men. Completed grades of schooling partially mediated the association between high-HAZ growth trajectory and scores on non-verbal fluid intelligence and working memory capacity.

**Conclusion:** Our findings extend the knowledge of the long-term associations between childhood linear growth on cognitive and socioemotional outcomes into mid-adulthood and suggest that schooling partially mediates the associations between linear growth and measures of cognitive ability.

**Keywords:** latent class growth analysis, longitudinal analysis, nutritional supplementation, executive functions, socioemotional functioning.

## 5.2 Introduction

Linear growth faltering in childhood, defined as lower length-or height than expected for age and sex, is one of the strongest correlates of poor cognitive and motor development, and school attainment (1-3). In low-and middle-income countries (LMICs), growth faltering takes place between conception and the child's second birthday, a period of rapid neurobehavioral development that has been coined "the first 1,000 days." Factors that adversely influence linear growth are well known and range from poverty, poor infant and young child feeding practices, inadequate childcare practices, and infections (4).

Studies in LMICs consistently show that growth faltering in the first 1,000 days is associated with poorer cognitive development and lower school attainment (1, 2, 5, 6). Among adults, longitudinal studies show that stunting in the first 1,000 days, defined as height-fo-age z scores (HAZ) < -2 SD below a reference population, is associated with lower performance on cognitive tests, increased probability of living in poverty, lower age at first birth and a higher number of pregnancies and children among women (3). It is also well established that after the first 1,000 days, growth faltering shows little if any association with human capital formation outcomes (1, 6). Some catch up in linear growth is possible after the first 1,000 days, but the cognitive gains remain unclear (7, 8).

Associations linking growth faltering in early childhood with socioemotional outcomes have received much less attention, partly because measures of socioemotional development are not routinely collected in applied research; thus, determinants have remained unknown (1).

Studies that have examined the long-term consequences of growth faltering in the first 1,000 days have used different methods to assess childhood linear growth. A common approach is to use mean height-for-age z-scores, measured at one point in time as the independent variable in studied models. However, this approach does not allow to describe the progression of linear growth over time, for which individual growth trajectories are required. Several studies have used conditional growth variables to assess deviations from a child's rate of change on linear growth, taking into account previous measures on the same child that would otherwise be correlated. However, most such publications have assumed that all children from a study sample are drawn from a single underlying population for which a single set of parameters can be estimated. The present study relaxes this assumption and accounts for the possibility that the sample might include multiple subpopulations characterized by different sets of parameters using Latent Class Growth Analysis (LCGA). LCGA accounts for correlated observations of HAZ on the same child and allows to categorize subjects into distinct subpopulations that follow common longitudinal trajectories of linear growth over time.

Using data from a nutritional supplementation trial in rural Guatemala implemented between 1969-1977 in 2,392 children at ages 0 to 84 months, and a follow-up study in 2017-2019, we aimed to: 1) examine the role of early-life characteristics on the pattern of height-for-age linear growth at ages 0 to 84 months; 2) investigate associations between longitudinal trajectories of height-for-age linear growth on non-verbal fluid intelligence, executive function (working memory, inhibitory control, and cognitive flexibility) and socioemotional functioning (happiness, life satisfaction, meaning and purpose and self-efficacy) at ages 40 to 57 years, and; 3) examine the mediating role of schooling on the association between height-for-age linear growth and adult cognitive outcomes.

## 5.3 Methods

### 5.3.1 Study Population

Data for this analysis come from the INCAP Nutritional Supplementation Trial conducted in four rural villages in eastern Guatemala between 1969-77, and two follow-up studies in 2015-17 and 2017-19.

The INCAP Nutritional Supplementation Trial was designed to test the effect of improved protein intake on physical and mental development in children < 7 years.
Two pairs of villages were matched for population size and one village from each pair was randomly assigned to receive atole, a gruel-type hot drink made from Incaparina (a dietary supplement mixture developed by INCAP) that contained 90 kcal and 6.4 gr of protein per 100 mL. The other two villages were assigned to receive fresco, a refreshing drink that contained 33 kcal and no protein per 100 mL. Both supplements were fortified with the same micronutrient concentrations by volume. The nutritional supplements were made available twice a day in a central location to all children ≤ 7 y and all pregnant and lactating women. All children ≤ 7 y were included at the beginning of the study, and all newborns were added during the duration of the study. Children were followed-up through age 7 y or until the end of the study, whichever came first. The final sample consisted of 2,392 study participants. In 2015-17 and 2017-19, participants were resurveyed. By 2015, information on coverage and attrition by 2017 is provided elsewhere (9). By 2017, of the original sample of 2,392 subjects, 385 had died, 255 had migrated abroad, and 109 were untraceable, resulting in 1,643 who were presumed alive and living in Guatemala and were eligible for enrollment. A total of 1,268 participants completed at

least one interview. For 1,499 participants, enough information was collected for inclusion for this study. All participants provided informed consent and the study was approved by the Institute of Nutrition of Central America and Panama (INCAP) and Emory University's Institutional Review Board at each study wave.

### 5.3.2 Data Collection and Variable Specification

#### *5.3.2.1 Infant and Child Anthropometry*

During the nutritional trial (1969-1977) length was measured at or near 15d, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 60, 72, and 84 months to the nearest 0.1 cm using length boards. To convert lengths to standing heights, we subtracted 1.0 cm from length measures obtained at 24 months and older (10). We converted heights into z scores of height-for age using the WHO growth standards (11, 12).

#### *5.3.2.2 Exposure to Nutritional Supplementation*

Birth years of study participants ranged from 1962 to 1977, and supplementation (atole or fresco) was provided from March 1, 1969, through February 28, 1977. Thus, exposure to supplementation occurred at different age windows for each child, prenatally through maternal consumption and postnatally through breastfeeding and the child own consumption. We categorized our study population into those that were exposed fully to supplementation during the first 1,000 days and those that received partial or no exposure to supplementation in the first 1,000 days. The interaction term between treatment assignment (atole or fresco) and age of exposure to nutritional supplementation (full exposure in first 1000 days vs. partial and no exposure) represents the differential effect of full exposure to atole in the first 1,000 days.

*5.3.2.3 Adult Cognitive Functioning*

In 2015-17 non-verbal fluid intelligence was assessed using sets A, B, and C of the Raven Progressive Matrices test for a possible total score of 36. Participants who did not complete a test in 2015-17 were administered a test in 2017-19. Final scores in both follow-up waves were collapsed and computed as the sum of correct responses. All other outcome measures hereinafter were assessed in 2017-19 follow-up. We measured executive function using three computerized version tests from the National Institutes of Health (NIH) Toolbox Cognition Battery, using touch screen tablet devices. We used the List Sorting Working Memory Tests to assess working memory (13).

The task requires participants to remember information that is visually and auditorily presented with illustrated pictures (either foods, animals or both) in size order from the smallest to the largest. Final scores are computed as the sum of correct responses across trials. Inhibitory control was assessed using the Flanker Inhibitory Control and Attention Test (14). The task requires respondents to focus on a central stimulus (arrow) while inhibiting attention to the flanking stimuli surrounding it (two arrows on each side). Cognitive flexibility was assessed using the Dimensional Change Card Sort Test (DCCS). In this task, two pictures that vary across shape and color are presented on a screen. Respondents are asked to switch between matching pictures by color and matching pictures by shape(14). For Flanker Inhibitory Control and

Attention and DCCS Tests, we used the NIH computed scores, which combine accuracy and reaction time (15).

*5.3.2.4 Adult Socioemotional Functioning*

Study participants were administered the Lyubomirsky scale of global subjective happiness (16) consisting of four items on a 5-point Likert scale, ranging from 1 (not a very happy person; Not at all) to 5 (A very happy person; A great deal). Final scores were computed as the mean of four items. We used the NIH Life Satisfaction survey to assess perceived global life satisfaction. The scale consists of five items, each answered on a 5-point Likert type scale ranging from 1= strongly disagree to 5= strongly agree (17). We computed the final scores as the sum of the 5 items. Purpose in life was assessed using the NIH Toolbox Meaning and Purpose Survey. Participants rated nine items on a 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree. The sum of the nine items served as the final score. To assess respondents' sense of global self-efficacy, we used the NIH Self-efficacy Survey. Ten items were rated on a 5-point Likert scale ranging from 1=never to 5=very often. Final scores were estimated as the sum of the ten items. For missing items on each scale, we applied a two-way imputation approach (18).

*5.3.2.5 Potentially Confounding Variables*

During the 1969-1977 trial, information on maternal characteristics (i.e., age at childbirth, height, and grades of schooling) was obtained by interview. A cumulative childhood household

SES score was created using principal component analysis using information derived from village censuses conducted in 1967 and 1975 (19). We categorized childhood SES into tertiles. We created dummy variables for each study village to capture village fixed characteristics. School attainment of study participants was ascertained by interview.

## 5.4 Statistical Analysis

### 5.4.1 Linear Growth Trajectories

Longitudinal data offer the possibility to study individual development over time. Latent class growth models allow for the identification of subgroups of individuals with distinct linear growth trajectories across the life course. We used Latent Class Growth Analysis (LCGA) to identify distinct linear growth trajectories in children at ages 0 to 84. In LCGA, subjects who share common longitudinal trajectories of observed HAZ scores are grouped into distinct latent classes. LCGA is a special case of growth mixture modeling where the variance and covariance of growth factors (slope and intercept) in each class are fixed to zero (20). Thus, within a given latent class, growth factors in each subject are equal.

To examine the role of exposure to nutritional supplementation in the first 1,000 days on linear growth, we also identified height-for-age z-scores trajectories in a subsample of the study population (children at ages 36 to 84 months). To ensure model stability we restricted the identification of trajectories to participants who had at least three-length measures collected between 0 to 84 months, and separately, between 36 to 84 months.

Length was measured every three months from birth to age 24 months, every six months from 24 to 48 months, and every year from 48 to 84 months. To account for the variability in the number of data points and their spacing, we further conducted a sensitivity analysis restricting the identification of linear growth trajectories to children with available HAZ at birth, 48 months, and at least one HAZ between birth and 48 months.

The optimal number of latent classes was determined by using Bayesian Information Criterion (BIC), entropy, the Lo-Medell-Rubin-Likelihood Ratio Test (LMR-LRT), Bootstrap Likelihood Ratio Test (BLRT) and posterior probability. We started with a two-class solution and added extra classes one at a time to assess if model fit statistics improved due to the additional class. This process ended when model fit statistics did not improve anymore. The solution that best fitted the data was the one with the lowest BIC value, highest entropy, significant LMR-LRT, and BLRT p-value, and the highest posterior probability (>0.70 for each class). The interpretability of classes and the number of subjects in each class were taken into consideration (no less than 5% of subjects for each class) (21).

The estimated classes were visually examined and arranged from high to low. Mean scores on cognitive and socioemotional measures were compared across trajectories using one-way analysis of variance.

### 5.4.2 Predictors of Linear Growth Trajectories

We examined predictors of linear growth trajectories in the period between 0 to 84 months and 36 to 84 months using multinomial logistic regression models. Models assessing predictors of linear growth trajectories between 0 to 84 months included household socioeconomic tertile in 1967-75, maternal age at birth of child, maternal education, and maternal height. All predictors were included in the same model stratifying by sex. We used multiple imputation for missing covariates. The proportion of missing information was 0.6% for maternal age at birth of the child, 3.2% for maternal education, and 8.6% for maternal height.

Models examining predictors of linear growth trajectories between 36 to 84 months included exposure to atole in the first 1,000 days (Model 1); household socioeconomic tertiles in 1967-75, maternal age at childbirth, maternal education, and maternal height (Model 2), and all components of model 1 and model 2 (Model 3). In all models, we controlled for fixed effects of birth village and birth year. Because a high proportion of participants were siblings, confidence intervals account for clustering at the household level.

### 5.4.3 Associations of HAZ Trajectories with Cognitive and Socioemotional Outcomes

We examined associations between HAZ linear growth trajectories derived between 0 to 84 months of age with measures of non-verbal fluid intelligence, executive function, and socioemotional capacities at ages 40 to 57 years using linear regression models. For both cognitive and socioemotional outcomes, the base model included a dummy variable for HAZ class membership (Model 1). We then added terms for exposure to supplementation in the first 1,000 days, supplement type, and the interaction term "exposure to atole in the first 1,000 days" (Model 2). We then added maternal characteristics of study participants (maternal age at birth of the child, maternal education, and maternal height), and household socioeconomic index in 1967-75 (Model 3). All models controlled for fixed effects of birth village and birth year and confidence intervals accounted for clustering of subjects within family. For covariates with missing values, we used multiple imputation techniques. We further conducted a sensitivity analysis to assess the consistency of our results with those obtained using conditional growth measures and HAZ at 24 months as predictors of adult cognitive outcomes.

The mediation analysis on the association between linear growth trajectories and adult cognitive outcomes was assessed using Structural Equation Modeling techniques with maximum likelihood with robust standard errors and chi-square (MLR) estimator. Mediation models adjusted for maternal height, fixed effects of birth village, birth year, household wealth index in 1969-77, age at intervention (full exposure in first 1000 days vs. partial and no exposure), and the interaction term specifying full exposure to atole (relative to fresco) in first 1000 days vs. partial and no exposure. Models additionally accounted for intra cluster correlation within family.

We used Mplus 8 for the identification of common longitudinal trajectories of height-for-age z-scores and the mediation analysis. All other analyses were conducted using Stata 15.

## 5.5 Results

Descriptive statistics of the study population are presented in **Table 5.1.** Based on model fit statistics**,** we identified three HAZ growth trajectories between 0 to 84 months, for both females and males **(Supplemental Table 5.1).** The estimated percentages, arranging the trajectories from high to low, were 34%, 50%, and 16%, among females, and 32%, 50%, and 18% among males (**Figure 5.1)**. In the period between 36 to 84 months, we identified two HAZ trajectories in females and three HAZ trajectories in males **(Supplemental Table 5.2 and**

**Supplemental Figure 5.1).** Trajectories assignment distributions remained similar between 0 to 84 months and 36 to 84 months **(Supplemental Tables 5.3 and 5.4).** Sensitivity analysis restricting the identification of trajectories to children with available data at birth, 48 months and at least one measure collected between birth to 48 months remained similar to those derived using other age windows **(Supplemental Figure 5.2).**

Mean scores on tests of adult cognitive function were higher among participants who attained higher linear growth (those in the high HAZ trajectory) at ages 0 to 84 months, particularly for tests assessing non-verbal fluid intelligence and working memory capacity. Differences in cognitive test scores between low and high HAZ trajectories were more pronounced in men relative to women **(Table 5.2).**

### 5.5.1 Predictors of Trajectory Class Membership

Results from multinomial logistic regression models showed that maternal height was positively associated with the likelihood of belonging to the high and medium HAZ trajectories relative to the low-HAZ trajectory among females (Relative Risk Ratio (RRR)= 1.21 95% CI: 1.14, 1.29, and RRR=1.10 95% CI: 1.05, 1.16) and males (RRR=1.20 95% CI: 1.14, 1.27, and RRR=1.11 95% CI: 1.05, 1.16), respectively. In addition, being in the wealthiest versus the poorest socioeconomic tertile was significantly associated with a higher likelihood of belonging to the high versus the low-HAZ trajectory in females (RRR = 2.88 95% CI: 1.41, 5.90), but not in males **(Table 5.3).**

For HAZ trajectories derived between 36 to 84 months, exposure to atole in the first 1,000 days was associated with a higher likelihood of belonging to the high-HAZ linear growth trajectory relative to the low HAZ trajectory among females (RRR= 2.9 95% CI: 1.26, 7.11) **(Supplemental Table 5.5).** In males, associations between exposure to atole in the first 1,000 days and higher likelihood of belonging to the high-HAZ linear growth trajectory were also positive but did not reach statistical significance **(Supplemental Table 5.6).** In both genders, maternal height was positively associated with high HAZ class membership (RRR=1.17 95% CI, 1.10, 1.23) in females, and (RRR=1.23 95% CI, 1.13, 1.34) in males.

### 5.5.2 Associations of HAZ Trajectories with Cognitive and Socioemotional Outcomes

**Table 5.4** shows the associations between HAZ linear growth trajectories and cognitive test scores. Models 1 to 3 were statistically indistinguishable; thus, we focus on findings from Model 3. In men, high- vs. low- HAZ trajectory was positively associated with Raven's Progressive Matrices (β=4.10, 95% CI: 2.49, 5.72), List Sorting working memory (β=1.73, 95% CI: 0.50, 2.96), Flanker inhibitory control and attention (β=0.65, 95% CI: 0.30, 0.98), and DCCS test scores (β=1.21, 95% CI: 0.67, 1.75). Associations between medium- vs. low- HAZ trajectory and cognitive test scores were also statistically significant but of lesser magnitude. In women, no significant associations were observed.

**Table 5.5** shows associations between HAZ growth trajectories and composite scores on scales assessing socioemotional capacities. In adjusted models in men, belonging to the high-HAZ linear growth trajectory was positively associated with higher scores on meaning and purpose (β=1.29, 95% CI:0.06, 2.52).

**Supplemental Table 5.7** shows results from the mediation analysis on the association between HAZ class membership and cognitive test scores through completed grades of schooling. Results for men indicated that the magnitude of the indirect effect through completed grades of schooling corresponded to 30% of the total effect of high latent class (vs. low class) on Raven's Progressive Matrices scores (Total effect Standardized (STD) β=0.64 95% CI, 0.29, 0.98, indirect effect through schooling STD β=0.19 95% CI, 0.02, 0.36), and 35% of the total effect of high latent class (vs. low class) on List Sorting working memory scores (Total effect STD β=0.45 95% CI, 0.02, 0.89, indirect effect through schooling STD β=0.16 95% CI, 0.02, 0.29). Similar associations but in lesser magnitude were observed between medium latent class (vs. low) and computed scores on Raven's Progressive Matrices and List Sorting working memory through completed grades of schooling. Models assessing mediation for Flanker inhibitory control and attention and DCCS tests did not converge.

Results from sensitivity analysis examining the association between conditional growth variables or HAZ at 24 months on cognitive and socioemotional outcomes were consistent with those with those derived using LCGA **(Supplemental Tables 5.8-5.11).**

## 5.6 Discussion

In this study, we used longitudinal data from rural Guatemala to identify distinct sex-specific post-natal height-for-age linear growth trajectories of children at ages 0-84 months. We identified predictors of those trajectories and examined its associations with adult cognitive and socioemotional outcomes.

We used LCGA that accounts for correlated observations of HAZ on the same child providing robust parameter estimates. In the period between 0 to 84 months, we identified three HAZ latent classes in both genders (low, medium, and high). In the period between 36 to 84 months, we identified two HAZ latent classes in females (low a high) and three in males (low, medium, and high). Observed patterns of linear growth throughout childhood are consistent with previous findings in LMICs, indicating that HAZ scores decrease from birth through age 2 with a modest recovery thereafter (22).

Our results indicate that linear growth trajectories show similar (parallel) slopes that are primarily distinguished as a matter of severity of linear growth faltering at birth (intercepts). The early differentiation of trajectories suggests that prenatal factors play a crucial role in stablishing life course linear growth. We found that maternal height significantly predicted linear growth trajectories at both age windows (0 to 84 and 36 to 84 months of age). The influence of maternal height in offspring's linear growth is thought to reflect a complex interplay between genetic characteristics, and intergenerational effects of the environment in which the mother grew up and developed (23). Short women (<145 cm) are also at higher risk of having small for gestational age (SGA) children, who, in turn, are more likely to suffer from stunted growth in early childhood (24, 25). The proposed biological mechanisms linking short maternal stature to SGA include low uterine volume and small pelvic size (25). We also found that high childhood SES was associated with an increased likelihood of high-HAZ latent class membership in the period between 0 to 84 months relative to the poorest SES tertile among females. In the period between 36 to 84 months, exposure to nutritional supplementation in the first 1,000 days was positively associated with an increased likelihood of high-HAZ linear growth membership in females. The effects of the nutritional intervention in males were also positive and favored membership to the high-HAZ linear growth trajectory but did not reach statistical significance. These results are consistent with previous analyses in this population, indicating that the nutritional intervention improved linear growth in both genders during the first 36 months, and most of the association was observed before age 2 y (26).

Taken together, we found modifiable and non-modifiable risk factors for early-life growth faltering. Modifiable risk factors included feeding practices and characteristics of the environment. Household socioeconomic status (SES) is a widely recognized determinant of growth faltering. Analysis of Demographic and Health Surveys in 72 low-income countries show that differences in stunting rates between poor and rich households are small in the first 5 months of life, becoming more pronounced thereafter (27). This period coincides with an age in which children are more directly exposed to the environment and living conditions. In order to have a positive impact on child development and growth, early-childhood intervention programs that can adequately address the behavioral change of caregivers are required. Researchers and intervention programs have moved toward changing behavior in psychosocial stimulation (through play and talk), feeding (quantity and quality of foods), and hygiene practices (handwashing) rather than tackling one problem alone (28). However, more local and governmental support and focalized resources are needed for these programs to yield better outcomes and be effective.

A key question to address given the similar (parallel) slopes found between linear growth trajectories was to examine whether associations between trajectories and study outcomes differ between linear growth in early versus later childhood. To address this question a sensitivity analysis was conducted using conditional growth variables, and separately, HAZ at or close to 24 months as predictors of adult cognitive and socioemotional functioning. Results using both approaches revealed that early rather than later linear growth, is more strongly and significantly associated with cognitive and socioemotional outcomes. Results from sensitivity analysis were also consistent with findings derived using LCGA techniques, which indicated that associations between trajectories and outcomes of interest were primarily distinguished as a matter of severity of linear growth faltering at birth. Moreover, all used analytical approaches testing whether linear growth trajectories, conditional growth variables, or HAZ at 24 months predicted cognitive and socioemotional outcomes showed positive associations in men but not in women, particularly for cognitive outcomes.

Proposed mechanisms of the effects of linear growth on cognitive and socioemotional outcomes include reduced motor activity, which is thought to limit the child's ability to explore the environment and receive psychosocial stimulation (1) reducing opportunities for the development of language, socioemotional and cognitive capacities (29). Another proposed mechanism involves reduced stimulation offered to short stature children due to caregivers' low expectations about their developmental potential (28). However, despite consistent associations between stunted growth and cognitive development, recent academic debate has suggested that these associations are unlikely to be causally related (30, 31). A more plausible explanation is that linear growth may be a marker of early-life neurobehavioral development (30) that remains intricately intertwined with both cognitive and socioemotional domains.

Our findings indicate important gender differences as observed associations between linear growth trajectories, cognitive, and socioemotional outcomes were significant only in men. In this prospective cohort, men completed more grades of schooling than women; thus, we assessed the mediation effect of schooling on the association between linear growth trajectories and cognitive outcomes. Results indicated that the association between high latent class (vs. low class) and cognitive scores found in men was partially mediated by completed grades of schooling, even after adjusting for socioeconomic factors. These findings are consistent with previous studies suggesting that children who complete more years of formal schooling score higher on measures of executive function (32, 33).

Adequate linear growth is an indicator of child health and a well-known determinant of childhood morbidity and mortality (34). It is possible that children in the high-HAZ trajectory may have also been healthier than those in the low HAZ trajectory. Healthy children are less likely to miss school, and as a result, have more opportunities to receive stimulation from teachers and peers. Studies suggest that school environments may provide unique opportunities for children to improve and exercise their executive function skills, particularly for those coming from less supportive home environments (35, 36).

The strengths of this study include the use of cohort longitudinal data with repeated growth measures from birth to age 7 years and cognitive and socioemotional measures with good psychometric properties collected in adulthood. Another strength is the use of LCGA, a highly flexible statistical technique that accounts for correlated measures and has higher statistical power than comparable methods (20). Despite its strengths, the use of LCGA also has limitations. Given that classification methods based on posterior class probability are never equal to one, the uncertainty of class assignment cannot be ruled out. Thus, caution is advised when interpreting the number of latent trajectories (37). Another limitation is the fact that we did not assess other prenatal and postnatal factors that are known to influence growth trajectories.

### 5.6.1 Conclusions

We identified a clear gradient of positive associations between childhood linear growth trajectories, cognitive and socioemotional outcomes in adulthood. Our results suggest that schooling partially mediates these associations. Maternal height, socioeconomic status, and exposure to nutritional supplementation in the first 1,000 days were significant predictors of high-HAZ latent class membership.

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**Table 5.1** Selected characteristics of study population (Mean ± SD or %) by sex. INCAP Nutritional Supplementation Trial longitudinal cohort.

| | Women (n=722) | Men (n=777) |
|---|---|---|
| Childhood household SES tertile, % | | |
| Poorest | 35.3 | 34.2 |
| Middle | 31.2 | 32.3 |
| Wealthiest | 33.5 | 33.5 |
| Maternal age, y | 27.5 ± 7.2 | 27.4 ± 7.1 |
| Maternal schooling, y | 1.3 ± 1.6 | 1.3 ± 1.5 |
| Maternal height | 148.5 ± 5.2 | 148.6 ± 5.2 |
| Completed years of schooling | 4.6 ± 3.5 | 5.4 ± 3.6 |
| HAZ latent class, % | | |
| Low | 15.6 | 18.0 |
| Medium | 50.0 | 49.9 |
| High | 34.3 | 32.0 |

Abbreviations: SES, socioeconomic status, HAZ Height for age-z-scores.

**Table 5. 2** Cognitive and socioemotional characteristics (Mean ± SD or %) of study population at ages 40-57 years by sex and childhood height for age-Z-scores latent trajectory class. INCAP Nutritional Supplementation Trial longitudinal cohort.

| | **Women (n=722)** | | | | **Men (n=777)** | | | |
|---|---|---|---|---|---|---|---|---|
| | High trajectory n=248, (34%) | Medium trajectory n=361, (50%) | Low trajectory n=113, (16%) | P-value[1] | High trajectory n=249, (32%) | Medium trajectory n=388, (50%) | Low trajectory n=140, (18%) | P value[1] |
| **Cognitive and executive functioning characteristics** | | | | | | | | |
| Raven Progressive Matrices score (out of 36) | 16.2 ± 5.0 | 15.2 ± 4.9 | 14.6 ± 4.5 | <0.05 | 20.4 ± 6.7 | 18.1 ± 5.5 | 15.8 ± 4.6 | <0.001 |
| List Sorting Working Memory score (out of 23) | 12.2 ± 3.6 | 11.2 ± 3.6 | 10.5 ± 3.8 | <0.01 | 13.6 ± 4.2 | 12.8 ± 3.7 | 11.6 ± 3.4 | <0.01 |
| Flanker Inhibitory Control and Attention computed score (out of 9) | 5.5 ± 1.0 | 5.4 ± 1.1 | 5.3 ± 1.1 | 0.21 | 6.1 ± 1.2 | 5.8 ± 1.2 | 5.4 ± 1.0 | <0.001 |
| DCCS[2] computed score (out of 9) | 5.3 ± 1.9 | 5.0 ± 1.9 | 4.9 ± 1.9 | 0.25 | 6.0 ± 1.8 | 5.6 ± 1.9 | 4.6 ± 1.8 | <0.001 |
| **Socioemotional functioning characteristics** | | | | | | | | |
| Lyubomirsky Happiness score (out of 5) | 4.2 ± 0.8 | 4.0 ± 1.0 | 4.0 ± 1.0 | 0.18 | 4.1 ± 0.8 | 4.2 ± 0.8 | 3.9 ± 0.8 | 0.05 |
| Life Satisfaction score (out of 25) | 18.7 ± 3.5 | 18.8 ± 3.3 | 18.2 ± 3.4 | 0.38 | 18.8 ± 3.5 | 19.2 ± 3.3 | 18.5 ± 3.7 | 0.23 |
| Meaning and Purpose score (out of 45) | 36.5 ± 3.8 | 36.3 ± 4.3 | 35.4 ± 3.6 | 0.13 | 37.8 ± 4.3 | 37.4 ± 3.8 | 36.4 ± 3.9 | 0.06 |
| Self-efficacy score (out of 40) | 31.2 ± 6.8 | 30.9 ± 7.2 | 30.8 ± 7.1 | 0.88 | 30.6 ± 6.5 | 32.2 ± 5.8 | 31.5 ± 7.1 | 0.08 |

[1] Based on one-way ANOVA

[2] Abbreviations: DCCS Dimensional Change Card Sort

**Table 5.3** Relative Risk Ratios (RRR) and 95% confidence intervals for predictors of height for age-z-scores latent trajectories between 0-84 months by sex. INCAP Nutritional Supplementation Trial longitudinal cohort.[1]

| | **Women (n=722)** | | **Men (n=777)** | |
|---|---|---|---|---|
| | **RRR** | **95% CI** | **RRR** | **95% CI** |
| **High- vs. low-HAZ latent class** | | | | |
| Childhood household SES tertile | | | | |
| Middle vs. poorest | 1.33 | 0.71, 2.49 | 1.18 | 0.64, 2.16 |
| Wealthiest vs. poorest | 2.88 | 1.41, 5.90** | 1.81 | 0.92, 3.56 |
| Maternal age at birth of child | 1.00 | 0.96, 1.03 | 1.02 | 0.98, 1.06 |
| Maternal years of schooling | 1.01 | 0.83, 1.22 | 1.05 | 0.88, 1.25 |
| Maternal height | 1.21 | 1.14, 1.29*** | 1.20 | 1.14, 1.27*** |
| **Medium- vs. low-HAZ latent class** | | | | |
| Childhood household SES tertile | | | | |
| Middle vs. poorest | 0.96 | 0.57, 1.62 | 1.16 | 0.70, 1.90 |
| Wealthiest vs. poorest | 1.52 | 0.79, 2.94 | 1.40 | 0.79, 2.48 |
| Maternal age at birth of child | 0.98 | 0.95, 1.01 | 0.99 | 0.97, 1.02 |
| Maternal years of schooling | 0.98 | 0.84, 1.15 | 0.97 | 0.83, 1.13 |
| Maternal height | 1.10 | 1.05, 1.16*** | 1.11 | 1.05, 1.16*** |

[1] Low-HAZ trajectory is the reference category. Estimates adjusted for fixed effects of birth village and birth year. For missing covariates, we used multiple imputation techniques. Confidence intervals account for clustering at the mother level. * P < 0.05. ** P < 0.01 *** P<0.001.

Abbreviations: SES, socioeconomic status, HAZ Height for age-z-scores.

**Table 5. 4** Associations of childhood height for age-z-scores latent trajectories and cognitive and executive functioning at ages 40-57 years by sex. INCAP Nutritional Supplementation Trial longitudinal cohort.[1]

| | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|
| | Medium- vs. Low- HAZ latent trajectory | | High- vs. low- HAZ latent trajectory | | Medium- vs. Low- HAZ latent trajectory | | High- vs. low- HAZ latent trajectory | |
| | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| Raven's Progressive Matrices | | | | | | | | |
| Model 1[a] | 0.40 | -0.76, 1.57 | 1.12 | -0.18, 2.43 | 2.29 | 1.00, 3.58** | 4.41 | 2.78, 6.04*** |
| Model 2[b] | 0.39 | -0.77, 1.56 | 1.16 | -0.15, 2.47 | 2.41 | 1.13, 3.68*** | 4.69 | 3.08, 6.31*** |
| Model 3[c] | 0.09 | -1.07, 1.25 | 0.48 | -0.84, 1.82 | 2.28 | 1.02, 3.54*** | 4.10 | 2.49, 5.72*** |
| List Sorting Working Memory | | | | | | | | |
| Model 1[a] | 0.56 | -0.43, 1.55 | 1.34 | 0.24, 2.42* | 1.24 | 0.31, 2.16** | 1.88 | 0.79, 2.98** |
| Model 2[b] | 0.62 | -0.36, 1.61 | 1.31 | 0.22, 2.40* | 1.24 | 0.32, 2.16** | 1.95 | 0.83, 3.07** |
| Model 3[c] | 0.48 | -0.49, 1.46 | 0.98 | -0.18, 2.16 | 1.18 | 0.21, 2.15* | 1.73 | 0.50, 2.96** |
| Flanker Inhibitory Control and Attention | | | | | | | | |
| Model 1[a] | 0.12 | -0.18, 0.42 | 0.15 | -0.17, 0.46 | 0.46 | 0.18, 0.75** | 0.68 | 0.36, 0.99*** |
| Model 2[b] | 0.12 | -0.19, 0.43 | 0.17 | -0.15, 0.49 | 0.48 | 0.20, 0.77** | 0.71 | 0.38, 1.03*** |
| Model 3[c] | 0.08 | -0.23, 0.39 | 0.06 | -0.26, 0.39 | 0.49 | 0.19, 0.77** | 0.65 | 0.30, 0.98*** |
| Dimensional Change Card Sort (DCCS) | | | | | | | | |
| Model 1[a] | -0.02 | -0.54, 0.50 | 0.07 | -0.51, 0.66 | 1.00 | 0.51, 1.49*** | 1.41 | 0.87, 1.95*** |
| Model 2[b] | -0.02 | -0.54, 0.51 | 0.11 | -0.47, 0.69 | 1.02 | 0.53, 1.50*** | 1.46 | 0.93, 2.00*** |
| Model 3[c] | -0.09 | -0.61, 0.42 | -0.01 | -0.59, 0.57 | 0.95 | 0.47, 1.43*** | 1.21 | 0.67, 1.75*** |

[1] Low-HAZ trajectory is the reference category. Sample sizes were 523 and 422 (Raven's Progressive Matrices), 468 and 390 (List Sorting Working Memory), 469 and 391 (Flanker Inhibitory Control and Attention), 475 and 395 (DCCS) for women and men, respectively.

[a] Adjusted for fixed effects of birth village and birth year

[b] Adjusted for fixed effects of birth village, birth year, exposure to supplementation in the first 1,000 days, and the interaction term specifying exposure to *Atole* in the first 1,000 days.

[c] Adjusted for fixed effects of birth village, birth year, exposure to supplementation in the first 1,000 days, the interaction term specifying exposure to *Atole* in the first 1,000 days, maternal age at birth of child (years, log-transformed), maternal years of schooling, maternal height (cm, log-transformed) and household socioeconomic status in 1967-75.

For missing covariates, we used multiple imputation techniques. Confidence intervals account for clustering at the mother level. * $P < 0.05$. ** $P < 0.01$ *** $P<0.001$.

**Table 5. 5** Associations of childhood Height for age-z-scores latent trajectories and socioemotional functioning at ages 40-57 years by sex. INCAP Nutritional Supplementation Trial longitudinal cohort.[1]

| | **Women** | | | | **Men** | | | |
|---|---|---|---|---|---|---|---|---|
| | Middle vs. low HAZ latent trajectory | | High vs. low HAZ latent trajectory | | Middle vs. low HAZ latent trajectory | | High vs. low HAZ latent trajectory | |
| | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| Happiness | | | | | | | | |
| Model 1[a] | 0.04 | -0.22, 0.30 | 0.24 | -0.04, 0.53 | 0.25 | 0.02, 0.49* | 0.13 | -0.13, 0.38 |
| Model 2[b] | 0.05 | -0.21, 0.31 | 0.23 | -0.05, 0.51 | 0.26 | 0.02, 0.50* | 0.14 | -0.12, 0.39 |
| Model 3[c] | 0.06 | -0.19, 0.33 | 0.28 | -0.03, 0.58 | 0.25 | 0.00, 0.50* | 0.12 | -0.15, 0.40 |
| Life satisfaction | | | | | | | | |
| Model 1[a] | 0.65 | -0.24, 1.54 | 0.69 | -0.31, 1.69 | 0.72 | -0.24, 1.68 | 0.41 | -0.67, 1.49 |
| Model 2[b] | 0.68 | -0.19, 1.56 | 0.64 | -0.34, 1.62 | 0.76 | -0.21, 1.73 | 0.47 | -0.63, 1.58 |
| Model 3[c] | 0.69 | -0.21, 1.60 | 0.70 | -0.36, 1.75 | 0.76 | -0.22, 1.75 | 0.38 | -0.78, 1.55 |
| Meaning and purpose | | | | | | | | |
| Model 1[a] | 0.87 | -0.14, 1.88 | 0.93 | -0.18, 2.05 | 0.91 | -0.16, 1.98 | 1.38 | 0.16, 2.60* |
| Model 2[b] | 0.83 | -0.19, 1.85 | 0.98 | -0.14, 2.11 | 0.94 | -0.11, 2.01 | 1.52 | 0.31, 2.72* |
| Model 3[c] | 0.76 | -0.27, 1.80 | 0.89 | -0.31, 2.08 | 0.88 | -0.18, 1.94 | 1.29 | 0.06, 2.52* |
| Self-efficacy | | | | | | | | |
| Model 1[a] | 0.23 | -1.63, 2.09 | 0.37 | -1.58, 2.33 | 0.65 | -1.12, 2.43 | -0.83 | -2.81, 1.13 |
| Model 2[b] | 0.17 | -1.71, 2.04 | 0.41 | -1.57, 2.39 | 0.69 | -1.11, 2.49 | -0.75 | -2.76, 1.26 |
| Model 3[c] | 0.41 | -1.46, 2.29 | 0.80 | -1.24, 2.85 | 0.63 | -1.18, 2.45 | -0.63 | -2.70, 1.44 |

[1] Sample sizes were 488 and 397 (Happiness), 487 and 397 (Life Satisfaction), 486 and 396 (Meaning and purpose), 486, and 396 (Self-efficacy) for women and men, respectively.

[a] Adjusted for fixed effects of birth village and birth year

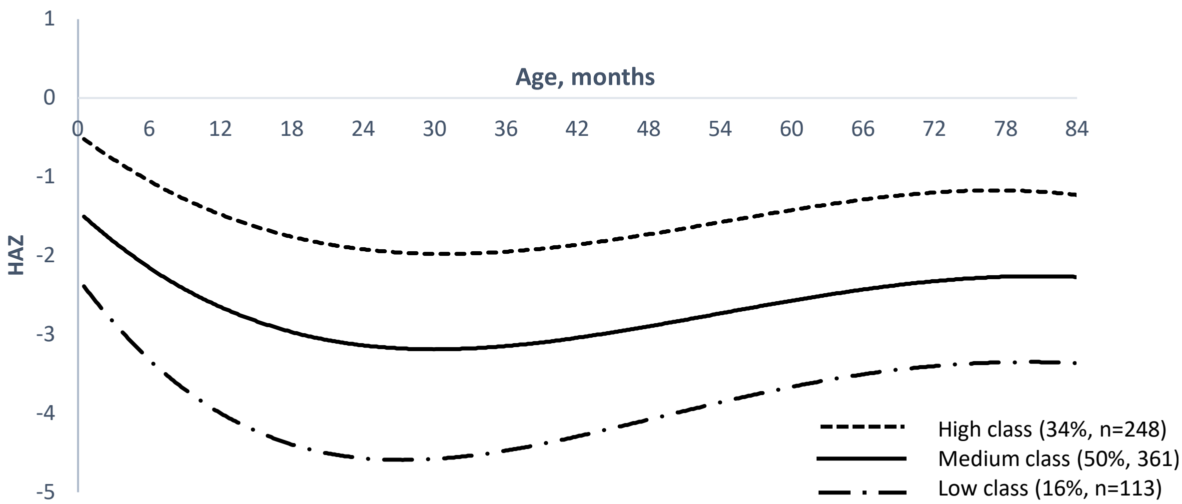
[b] Adjusted for fixed effects of birth village, birth year, exposure to supplementation in the first 1,000 days, and the interaction term specifying exposure to *Atole* in the first 1,000 days.

[c] Adjusted for fixed effects of birth village, birth year, exposure to supplementation in the first 1,000 days, the interaction term specifying exposure to *Atole* in the first 1,000 days, maternal age at birth of child (years, log-transformed), maternal years of schooling, maternal height (cm, log-transformed) and household socioeconomic status in 1967-75.

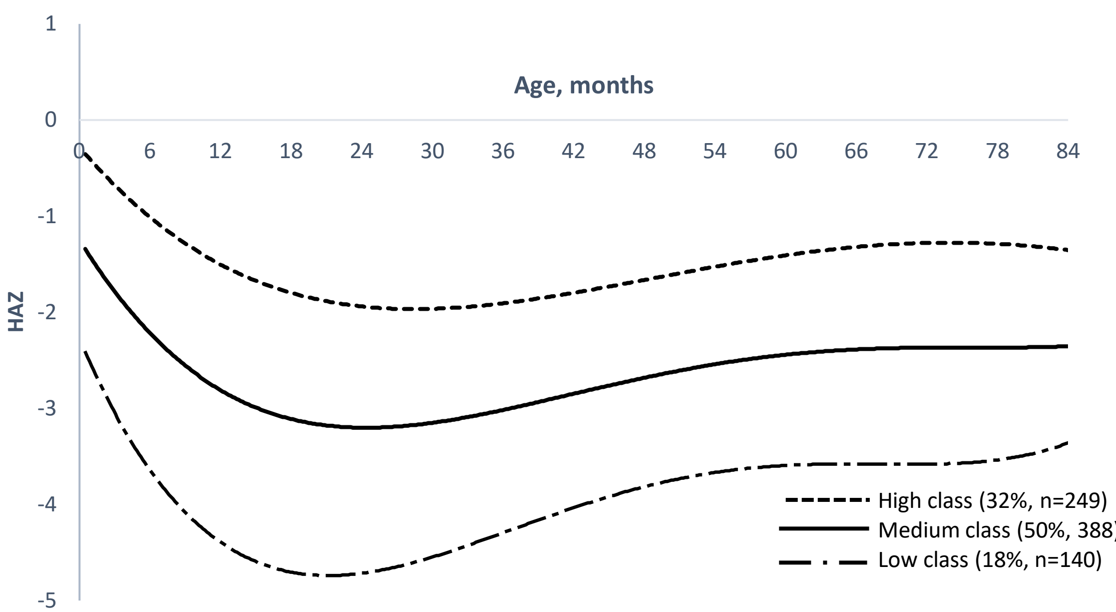
For missing covariates, we used multiple imputation techniques. Confidence intervals account for clustering at the mother level.
* $P < 0.05$.

**Figure 5. 1** Height for age-z-scores latent trajectories from birth through 84 months in women (A) and men (B). INCAP Nutritional Supplementation Trial longitudinal cohort.

**A)**




**B)**



**Supplemental Table 5.1** Fit Statistics of Unconditional Candidate Latent Class Growth Models 0-84 months, by sex

| | Females (*n* = 722) | | | Males (*n* =777) | | |
|---|---|---|---|---|---|---|
| **Fit Statistics** | 2 Class | 3 Class | 4 Class | 2 Class | 3 Class | 4 Class |
| BIC | 16915 | 15653 | 15114 | 20028 | 18569 | 17976 |
| Entropy | 0.87 | 0.89 | 0.85 | 0.86 | 0.89 | 0.91 |
| LMR, *P* value | <0.001 | <0.001 | 0.10 | 0.04 | <0.01 | 0.35 |
| LRT, P value | <0.001 | <0.001 | 0.11 | 0.05 | <0.01 | 0.36 |
| BLRT, *P* value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BIC, Bayesian Information Criterion; LMR, Lo-Mendell-Rubin Likelihood Ratio Test; LRT, Lo-Mendell-Rubin Adjusted Test; BLRT, Bootstrap Likelihood Ratio Test.

**Supplemental Table 5.2** Fit Statistics of Unconditional Candidate Latent Class Growth Models 36-84 months, by Sex, in the INCAP Nutrition Supplementation Trial Longitudinal Cohort.

| | Females (*n* =425) | | | Males (*n* =476) | | |
|---|---|---|---|---|---|---|
| **Fit Statistics** | 2 Class | 3 Class | 4 Class | 2 Class | 3 Class | 4 Class |
| BIC | 4368 | 3605 | 3153 | 4654 | 3889 | 3472 |
| Entropy | 0.85 | 0.92 | 0.92 | 0.86 | 0.92 | 0.92 |
| LMR, *P*-value | 0.04 | 0.08 | 0.12 | 0.02 | <0.01 | 0.12 |
| LRT, P-value | 0.05 | 0.08 | 0.13 | 0.02 | <0.01 | 0.13 |
| BLRT, *P* value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BIC, Bayesian Information Criterion; LMR, Lo-Mendell-Rubin Likelihood Ratio Test; LRT, Lo-Mendell-Rubin Adjusted Test; BLRT, Bootstrap Likelihood Ratio Test.

**Supplemental Table 5. 3** Trajectories assignment distributions between 0-84 months and 36 to 84 months in women, n=425

| | | **36-84 months** | | **Total** |
|---|---|---|---|---|
| | | High class | Low class | |
| **0-84 months** | High class | 28.9 | 0 | 28.9 |
| | Medium class | 29.4 | 24.2 | 53.6 |
| | Low class | 0 | 17.4 | 17.4 |
| **Total** | | 58.3 | 41.6 | 100 |

**Supplemental Table 5. 4** Trajectories assignment distributions between 0-84 months and 36 to 84 months in men, n=476

| | | **36-84 months** | | | **Total** |
|---|---|---|---|---|---|
| | | High class | Medium class | Low class | |
| **0-84 months** | High class | 21.8 | 5.2 | 0 | 27.1 |
| | Medium class | 2.9 | 42.9 | 6.9 | 52.7 |
| | Low class | 0 | 2.5 | 17.6 | 20.2 |
| **Total** | | 24.9 | 50.6 | 24.5 | 100 |

**Supplemental Table 5.5** Relative Risk Ratios (RRR) and 95% confidence intervals for predictors of height for age-z-scores latent trajectories between 36 to 84 months in women. INCAP Nutritional Supplementation Trial longitudinal cohort.[1]

| | Women (n=425) | | |
|---|---|---|---|
| | **Model 1** | **Model 2** | **Model 3** |
| **High- vs. low-HAZ latent class** | | | |
| Exposure to *Atole* in full first 1,000 days. | 2.30 (1.02,5.18)* | | 2.99 (1.26, 7.11)* |
| Childhood household SES tertile | | | |
| Middle vs. poorest | | 1.39 (0.78, 2.45) | 1.37 (0.76, 2.43) |
| Wealthiest vs. poorest | | 1.48 (0.80, 2.76) | 1.51 (0.81, 2.82) |
| Maternal age at birth of child | | 0.99 (0.96, 1.02) | 0.98 (0.95, 1.02) |
| Maternal years of schooling | | 0.98 (0.84, 1.14) | 0.98 (0.84, 1.14) |
| Maternal height | | 1.16 (1.09, 1.23)*** | 1.17 (1.10, 1.23)*** |

[1] Estimates adjusted for fixed effects of birth village and birth year. For missing covariates, we used multiple imputation techniques. Confidence intervals account for clustering at the mother level.

* P < 0.05. ** P < 0.01 *** P<0.001.

Abbreviations: SES, socioeconomic status, HAZ Height for age-Z-scores.

**Supplemental Table 5. 6** Relative Risk Ratios (RRR) and 95% confidence intervals for predictors of height for age-z-scores latent trajectories between 36 to 84 months in men. INCAP Nutritional Supplementation Trial longitudinal cohort. [1]

| | Men (n=476) | | |
|---|---|---|---|
| | **Model 1** | **Model 2** | **Model 3** |
| **High- vs. low-HAZ latent class** | | | |
| Exposure to *Atole* in full first 1,000 days. | 1.35 (0.49, 3.74) | | 1.65 (0.52, 5.20) |
| Childhood household SES tertile | | | |
| Middle vs. poorest | | 0.97 (0.44, 2.15) | 1.03 (0.45, 2.32) |
| Wealthiest vs. poorest | | 2.15 (0.90, 5.17) | 2.27 (0.93, 5.51) |
| Maternal age at birth of child | | 1.04 (0.99, 1.09) | 1.04 (0.99, 1.09) |
| Maternal years of schooling | | 0.99 (0.79, 1.22) | 0.98 (0.78, 1.22) |
| Maternal height | | 1.23 (1.12, 1.34)*** | 1.23 (1.13, 1.34)*** |
| **Medium- vs. low-HAZ latent class** | | | |
| Exposure to *Atole* in full first 1,000 days. | 1.87 (0.76, 4.62) | | 2.21 (0.84, 5.81) |
| Childhood household SES tertile | | | |
| Middle vs. poorest | | 1.06 (0.57, 1.95) | 1.13 (0.60, 2.13) |
| Wealthiest vs. poorest | | 1.70 (0.87, 3.31) | 1.82 (0.92, 3.58) |
| Maternal age at birth of child | | 0.99 (0.96, 1.03) | 0.99 (0.96, 1.03) |
| Maternal years of schooling | | 0.98 (0.82, 1.17) | 0.96 (0.90, 1.16) |
| Maternal height | | 1.12 (1.05, 1.20)** | 1.12 (1.05, 1.20)** |

[1] Estimates adjusted for fixed effects of birth village and birth year. For missing covariates, we used multiple imputation techniques. Confidence intervals account for clustering at the mother level. * P < 0.05. ** P < 0.01 *** P<0.001.

Abbreviations: SES, socioeconomic status, HAZ Height for age-Z-scores.

**Supplemental Table 5. 7** Mediation analysis of the association between Height for age-Z-scores latent trajectories through age 7 years in raven scores (A) and working memory scores (B) in males. INCAP Nutritional Supplementation Trial longitudinal cohort [1]

| Type of effect | Raven's Progressive Matrices score [2] | List Sorting working memory score [3] |
|---|---|---|
| **High HAZ latent class vs. low class** | | |
| Total effect | 0.64 (0.29, 0.98) ** | 0.45 (0.02, 0.89) ** |
| Indirect effect via schooling | 0.19 (0.02, 0.36) ** | 0.16 (0.02, 0.29) ** |
| Direct effect | 0.45 (0.12, 0.77) ** | 0.29 (-0.12, 0.72) |
| **Medium HAZ class vs. low class** | | |
| Total effect | 0.38 (0.11, 0.65) ** | 0.32 (-0.02, 0.67) * |
| Indirect effect via schooling | 0.15 (0.01, 0.27) ** | 0.11 (0.01, 0.22) ** |
| Direct effect | 0.23 (-0.01, 0.48) * | 0.21 (-0.12, 0.54) |

1. Values are standardized coefficients (STDY in Mplus), and 95% Confidence Intervals interpreted as the change in *Y* in *Y* standard deviation units when *X* changes from 0 to 1. *p<0.05, **p<0.01.
2. Sample size was 514. Estimates adjusted for maternal height, fixed effects of birth village, birth year, household wealth index in 1969-77, age at intervention (full exposure in first 1000 d vs. partial and no exposure), and the interaction term specifying full exposure to atole (relative to fresco) in first 1000 d vs. partial and no exposure. Model fit statistics: RMSEA=0, CFI=1 TLI=1.
3. Sample size was 506. Estimates adjusted for maternal height, fixed effects of birth village, birth year, household wealth index in 1969-77, age at intervention (full exposure in first 1000 d vs. partial and no exposure), and the interaction term specifying full exposure to atole (relative to fresco) in first 1000 d vs. partial and no exposure. Model fit statistics: RMSEA=0, CFI=1 TLI=1.

**Supplemental Table 5. 8** Change in cognitive test scores (SD) per SD change in conditional growth variable.[1]

| | Non-verbal fluid intelligence | | | Working memory | | | Inhibitory control | | | Cognitive flexibility | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Pooled** | **Women** | **Men** | **Pooled** | **Women** | **Men** | **Pooled** | **Women** | **Men** | **Pooled** | **Women** | **Men** |
| Birth length Z score | 0.08 (-0.02, 0.18) | 0.01 (-0.15, 0.17) | 0.16 (0.04, 0.28) ** | 0.06 (-0.05, 0.17) | 0.04 (-0.12, 0.21) | 0.07 (-0.08, 0.22) | 0.13 (0.03, 0.24) * | 0.12 (-0.04, 0.28) | 0.17 (0.01, 0.32) * | 0.10 (-0.01, 0.20) | -0.01 (-0.20, 0.17) | 0.20 (0.08, 0.31) ** |
| Conditional length at 24 mo | 0.04 (-0.09, 0.18) | -0.12 (-0.32, 0.08) | 0.24 (0.03, 0.45) * | 0.08 (-0.06, 0.22) | -0.02 (-0.22, 0.17) | 0.18 (-0.06, 0.42) | 0.01 (-0.11, 0.14) | -0.04 (-0.23, 0.15) | 0.01 (-0.22, 0.23) | 0.12 (-0.02, 0.25) | 0.02 (-0.21, 0.25) | 0.15 (-0.02, 0.33) |
| Conditional length at mid-childhood | -0.08 (-0.20, 0.05) | -0.09 (-0.31, 0.12) | -0.05 (-0.19, 0.09) | -0.06 (-0.22, 0.10) | -0.11 (-0.31, 0.10) | -0.05 (-0.35, 0.24) | -0.01 (-0.15, 0.13) | -0.07 (-0.25, 0.12) | 0.01 (-0.22, 0.25) | -0.10 (-0.21, 0.01) | -0.06 (-0.28, 0.15) | -0.09 (-0.20, 0.02) |

[1] Data are beta coefficients (95% Confidence Intervals (CI)) from linear regression models. Sample sizes are 128 and 105 for non-verbal fluid intelligence, 119 and 100 for working memory, 120 and 100 for inhibitory control, 118 and 102 for cognitive flexibility in women and men, respectively. Models adjusted for log of maternal age at birth of child, log of maternal height, maternal education, early-life socioeconomic status, fixed effects of birth village, sex, year of birth and the nutritional intervention. CI account for intra cluster correlation at the household level. * p<0.05 ** p<0.01

**Supplemental Table 5. 9** Change in socioemotional scale scores (SD) per SD change in conditional growth variable.[1]

| | Happiness | | | Life Satisfaction | | | Meaning and Purpose | | | Self-efficacy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Pooled** | **Women** | **Men** | **Pooled** | **Women** | **Men** | **Pooled** | **Women** | **Men** | **Pooled** | **Women** | **Men** |
| Birth length Z score | 0.11 (-0.01, 0.24) | 0.06 (-0.13, 0.24) | 0.14 (-0.02, 0.31) | 0.17 (0.05, 0.28) ** | 0.14 (-0.03, 0.32) | 0.18 (0.01, 0.34) * | 0.10 (0.00, 0.19) * | 0.12 (-0.02, 0.25) | 0.12 (-0.02, 0.26) | -0.01 (-0.12, 0.09) | 0.04 (-0.15, 0.23) | -0.06 (-0.18, 0.06) |
| Conditional length at 24 mo | 0.06 (-0.06, 0.18) | 0.15 (-0.03, 0.34) | -0.01 (-0.19, 0.17) | -0.05 (-0.18, 0.08) | 0.01 (-0.17, 0.19) | -0.15 (-0.35, 0.07) | -0.03 (-0.18, 0.12) | -0.19 (-0.39, 0.01) | 0.05 (-0.18, 0.29) | -0.04 (-0.19, 0.10) | -0.03 (-0.23, 0.17) | -0.02 (-0.23, 0.19) |
| Conditional length at mid-childhood | 0.03 (-0.08, 0.16) | -0.09 (-0.32, 0.13) | 0.12 (0.01, 0.23) * | -0.14 (-0.26, -0.02) * | -0.16 (-0.39, 0.06) | -0.13 (-0.27, 0.01) | -0.11 (-0.22, -0.01) | -0.14 (-0.35, 0.06) | -0.11 (-0.26, 0.05) | -0.08 (-0.21, 0.05) | -0.04 (-0.27, 0.17) | -0.11 (-0.27, 0.04) |

[1] Data are beta coefficients (95% CI) from linear regression models. Sample sizes for all outcomes are 121 for women and 100 for men. Models adjusted for log of maternal age at birth of child, log of maternal height, maternal education, early-life socioeconomic status, fixed effects of birth village, sex, year of birth and the nutritional intervention. Confidence intervals account for intra cluster correlation at the household level. * p<0.05 ** p<0.01

**Supplemental Table 5.10** Early-life growth failure (HAZ 24 months) and adult cognitive outcomes by sex

| | **Pooled** | **Women** | **Men** |
|---|---|---|---|
| Non-verbal fluid intelligence | 0.61<br>(0.26, 0.96) ** | 0.34<br>(-0.07, 0.75) | 0.93<br>(0.39, 1.48) ** |
| Working memory | 0.55<br>(0.29, 0.80) ** | 0.59<br>(0.25, 0.93) ** | 0.51<br>(0.15, 0.87) ** |
| Inhibitory control | 0.14<br>(0.06, 0.21) ** | 0.04<br>(-0.05, 0.13) | 0.24<br>(0.13, 0.34) ** |
| Cognitive flexibility | 0.24<br>(0.11, 0.36) ** | 0.13<br>(-0.05, 0.30) | 0.35<br>(0.18, 0.51) ** |

Data are beta coefficients (95% CI) from linear regression models. Sample size is 647 and 515 for non-verbal fluid intelligence, 579 and 478 for working memory, 580 and 477 for inhibitory control, and 589 and 482 for DCCS in women and men, respectively.

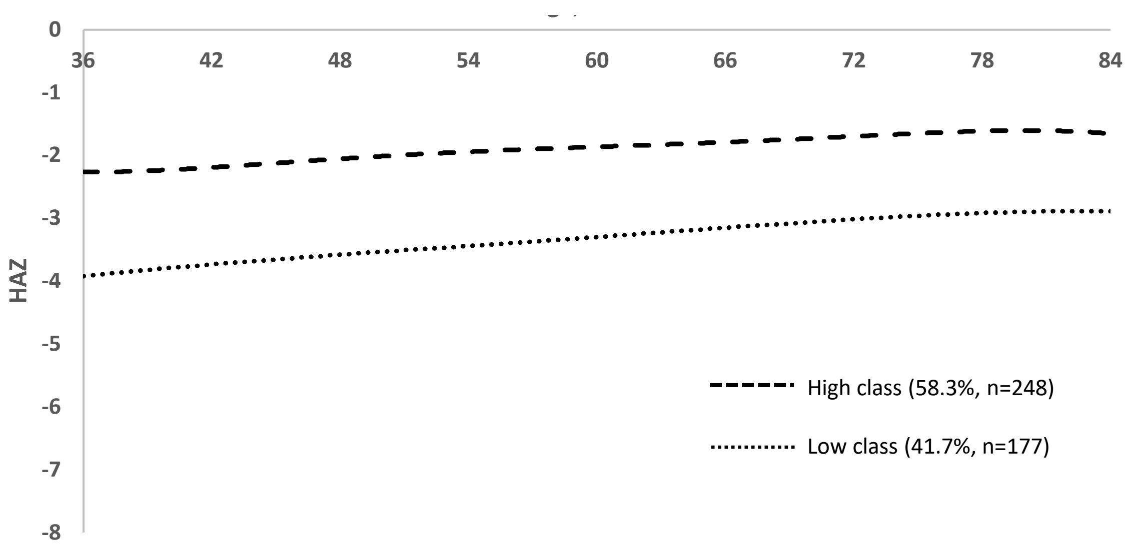
**Supplemental Table 5.11** Early-life growth failure (HAZ 24 months) and adult socioemotional outcomes by sex

| | **Pooled** | **Women** | **Men** |
|---|---|---|---|
| Happiness | 0.05<br>(-0.00, 0.11) | 0.08<br>(0.00, 0.17) * | 0.02<br>(-0.07, 0.10) |
| Life Satisfaction | 0.13<br>(-0.09, 0.36) | 0.18<br>(-0.11, 0.48) | 0.07<br>(-0.25, 0.38) |
| Meaning and purpose | 0.27<br>(0.02, 0.52) * | 0.19<br>(-0.16, 0.53) | 0.33<br>(-0.04, 0.70) |
| Self-efficacy | 0.15<br>(-0.26, 0.57) | 0.47<br>(-0.12, 1.06) | -0.16<br>(-0.77, 0.45) |

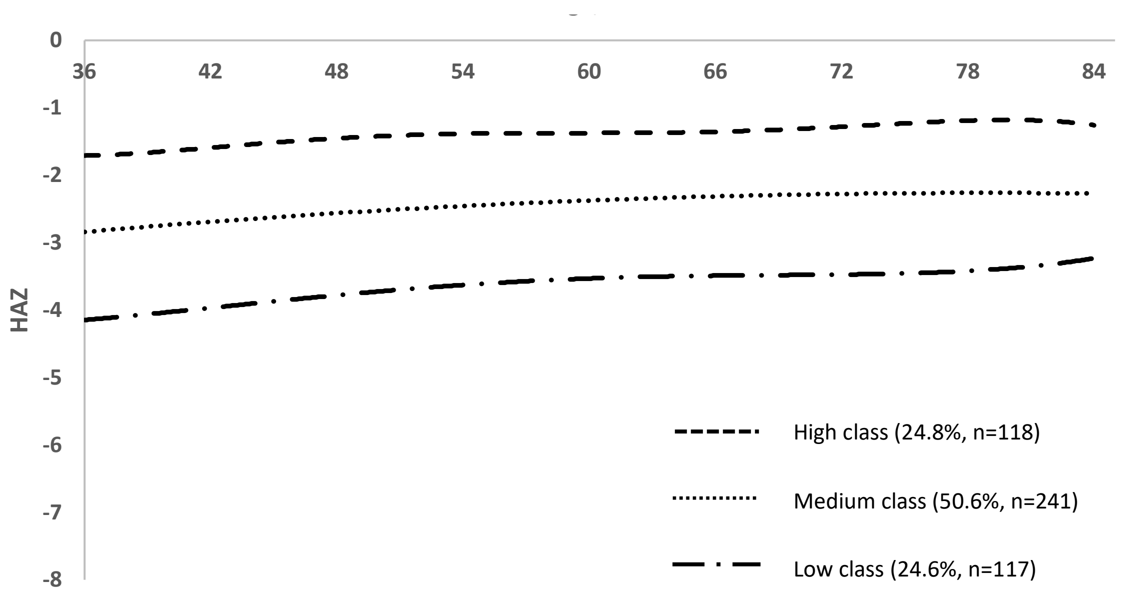
Data are beta coefficients (95% CI) from linear regression models. Sample size is 607 and 487 for happiness, 606 and 487 for life satisfaction, 605 and 486 for meaning and purpose, and 605 and 486 for self-efficacy in women and men, respectively.

**Supplemental Figure 5.1** Height for age-z-scores latent trajectories from 36 to 84 months in women (A) and men (B). INCAP Nutritional Supplementation Trial longitudinal cohort.

**A)**




**B)**



**Supplemental Figure 5. 2** Height for age-z-scores latent trajectories in children with length measures at birth, 48 months and at least one measure collected between birth and 48 months, n=285

**CHAPTER 6:** Cross-sectional interrelationships between cognitive and socio-emotional functioning in Guatemalan adults

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## 6.1 Abstract

**Background:** Associations between cognitive and socioemotional factors are understudied in low-and-middle-income countries (LMICs). We aimed to determine the cross-sectional interrelationships between psychological wellbeing, social support, spirituality and religion, mental health, intelligence and executive function among adults in Guatemala and examine whether associations differ across gender.

**Methods:** From Dec 2017 to Apr 2019 data were collected from 704 women and 564 men between the ages of 40-57 y in four rural communities in eastern Guatemala and Guatemala City. We used Confirmatory Factor Analysis (CFA) under the Structural Equation Modeling (SEM) framework to examine whether the established dimensionality and factor-loadings patterns for latent domains fitted our sample population. We estimated crossectional intercorrelations between latent domains (i.e., psychological wellbeing, spirituality and religion, emotional support, executive function) and observed measures of intelligence and mental health.

**Results:** CFA supported the construct validity of first order and second-order factor structures. We found strong positive correlations between spirituality and religion and psychological wellbeing and between measures of intelligence and executive function. All other intercorrelations showed small to medium effect sizes.

**Conclusions:** Spiritual and religious involvement may play an important role in promoting higher levels of psychological wellbeing and executive function in our study population. The directionality of these associations remains to be further explored.

**Keywords:** Psychological well-being, executive function, spirituality, general intelligence, mental health, social support, structural equation modeling.

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## 6.2 Background

Much evidence suggests that the skills that contribute to achieving lifelong wellbeing rely on a set of higher-order cognitive processes: general intelligence and executive function. General intelligence, usually measured with intelligence quotient (IQ) tests, is the ability to acquire knowledge and use it in novel ways (1). Executive function refers to the cognitive process responsible for the conscious ability to control and regulate thoughts, emotions, and behavior in pursuit of personal goals (2). Working memory, inhibitory control, and cognitive flexibility have been identified as the building blocks of executive function, which together are required for higher-level executive functioning (2, 3).

The positive association of IQ and executive function on social outcomes is well documented. Studies have consistently shown that higher IQ predicts better income (4), lower mortality and morbidity (5, 6) and reduced criminal and delinquent involvement (7, 8). Similarly, studies have documented that a measure of childhood self-control (a composite score that included observational ratings of children's lack of control of parent and teacher reports on children's impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity) predicts better physical health, higher income, lower substance abuse, and criminal offending outcomes even after accounting for IQ, gender, and other social characteristics (9). Moreover, individuals with higher self-control are happier and experience greater life satisfaction than those with poor self-control (10).

The evidence on the influence of coping resources such as social support and spiritual and religious involvement on promoting physical and psychological wellbeing is accumulating. The phenomena of social support have primarily been studied in the context of physical health with studies reporting inverse associations between the quality and quantity of social networks and risk of mortality (11). Moreover, social support has been positively linked with mental health, with some evidence indicating that this association varies across gender and life stage (12).

Studies on the influence of spiritual and religious involvement on quality of life have shown that people who tend to have religious or spiritually-related emotions, such as a sense of "connectedness" or "transcendence" adapt better to stressful life events (13), report lower levels of depression and substance abuse (14), have higher levels of social support (15) and report lower cardiovascular disease and hypertension (16).

Most evidence on the influence of intelligence and executive function on wellbeing derives from studies conducted in developed countries. Moreover, much research investigating the role of coping resources on promoting wellbeing originates from populations experiencing medical conditions, disabilities or the elderly. There is little information on the interrelationships between cognitive and socioemotional capacities, particularly among non-clinical populations living of low-and middle-income countries (LMICs). The examination of these factors, particularly in populations living in poor-resource settings of LMICs is important as it can provide unique insights into the interplay of these processes in contexts of adversity.

This study aims to determine the cross-sectional interrelationships between cognitive and socioemotional capacities, namely psychological wellbeing, social support, spirituality and religion, mental health, intelligence and executive function among adults in Guatemala and examine whether these associations differ across gender.

## 6.3 Methods

### 6.3.1 Study Population and Setting

The population in our study participated in a community-randomized food supplementation trial in early childhood. The intervention was implemented between 1969-1977 by the Institute of Nutrition of Central America and Panama (INCAP) in 4 rural communities in eastern Guatemala. At the time of the intervention, child malnutrition and infectious diseases were endemic in the study villages and most adults were illiterate (17). The nutritional trial was designed to assess the impact of improved nutrition on child growth and cognitive development. Complete details of the original trial and subsequent follow-up studies are published elsewhere (18, 19).

### 6.3.2 Training and Data Collection

Data were collected from Dec 2017 to Apr 2019 in 1268 participants at ages 40-57 y residing in the original study villages and Guatemala City. Enumerators were trained on the correct administration of cognitive tests and socio-emotional measures. The survey instruments were piloted before the commencement of the study for cultural appropriateness. Participants were interviewed in a research facility established in a rented building in the village. For subjects living in other parts of Guatemala, cognitive tests and questionnaires were administered in the INCAP headquarters in Guatemala City. Further details on training, adaptation, and administration of the cognitive test are published elsewhere (20).

The Institutional Review Boards of Emory University (Atlanta, GA) and INCAP (Guatemala City, Guatemala) gave ethical approval for this study. All participants gave written informed consent.

### 6.3.3 Measurements

#### *6.3.3.1 Executive Function*

We measured executive function as a unitary construct that includes working memory, inhibitory control, and cognitive flexibility as building blocks (3, 21). Executive function tests were administered using touch screen tablet devices. We assessed working memory with the computerized Spanish-language version of the NIH Toolbox List Sorting Working Memory Test (22). The task requires participants to remember information that is visually and auditorily presented with illustrated pictures (either foods, animals or both) in size order from the smallest to the largest . The sum of correct responses served as the primary measure.

Inhibitory Control was evaluated with the computerized Spanish-language version of the NIH Toolbox Flanker Inhibitory Control and Attention Test (23). The task requires participants to indicate the left-right orientation of a centrally presented stimulus, inhibiting potentially irrelevant information from the flanking stimuli (24). Cognitive flexibility was measured with the computerized Spanish-language version of the NIH Dimensional Change Card Sort (DCCS) Test. In this task, participants were asked to switch between matching pictures by color and matching pictures by shape (23). For Flanker Inhibitory Control and Attention and DCCS Tests, we used the NIH toolbox computed scores which uses a two-vector algorithm which combines accuracy and reaction time (25).

*6.3.3.2 Non-verbal Fluid Intelligence (IQ)*

We assessed non-verbal fluid intelligence using the Raven's Progressive Matrices Test (26). The test consists of a pattern, for which there is a piece missing. Participants were asked to select which piece complete the pattern from a number of options. Three of the five scales (A, B and C, with 12 questions each, for a maximum possible score of 36) were administered since previous applications in this population show that few participants were able to progress beyond the third scale. The sum of correct responses served as the primary measure.

*6.3.3.3 Psychological Wellbeing*

Wellbeing is a multidimensional construct that refers to optimal psychological functioning and experience with implications in physical, socioemotional and mental aspects (27, 28). The hedonic approach defines wellbeing in terms of pleasure attainment and pain avoidance and the eudaimonic approach defines it in terms of psychosocial functioning. We adopted a model on psychological wellbeing that captures both hedonic (e.g., happiness and life satisfaction) and eudaimonic aspects (e.g., meaning and purpose and self-efficacy) (27, 29, 30).

We assessed happiness with the use of the Lyubomirsky Scale of Global Subjective Happiness (31). Participants were asked to rate four items on a 5-point Likert scale ranging from 1 (Very unhappy) or (Not at all) to 5 (Very happy) or (A great deal). Item 4 is reverse scored. A total score is calculated by computing a mean of the 4 items. Life satisfaction was measured by the NIH Toolbox General Life Satisfaction Survey (32) consisting of 5 items assessing global feelings and attitudes about one's life. Participants rated these items on a 5-point Likert scale ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). Item 3 used reverse scoring. Self-efficacy, defined as a person's belief in his/her capacity to manage, function and have control over meaningful events (33), was assessed using the NIH Toolbox Self-Efficacy Survey (34). Participants rated ten items on a 5-point Likert scale ranging from 1 (Never) to 5 (Very often). Purpose in life was measured using the NIH Toolbox Meaning and Purpose Survey. Participants rated nine items on a 5-point Likert scale ranging from 1 (Strongly disagree) to 5 (Strongly agree) (32). All items used positive scoring except items 5 and 9 which were reverse scored.

In all scales with missing items, we applied a two-way imputation approach (35). We calculated the final scores for each scale as the sum of the item scores on that scale. All negatively framed items were reversed coded, so that all in all scales higher scores represent higher levels of socioemotional functioning for each measured domain. For all socio-emotional scales with missing items, we applied a two-way imputation approach (35).

*6.3.3.4 Emotional Support*

Emotional support is one component of social support that refers to the experience of being cared about, valued and loved by people in one’s social network (36). We assessed emotional support with the fixed 8-item form of the NIH Toolbox Emotional Support Survey (37). Each item administered has a 5-point Likert scale. Computed scores were estimated as the sum of all items.

*6.3.3.5 Spirituality and Religion*

While the terms spirituality and religion are used interchangeably, they entail different meanings. Religion functions in the context of an organized institution that places spirituality under a specific set of beliefs, values, and practices. Spirituality, on the other hand, is a subjective experience that involves a sense of connection and transcendence with a greater force (38). Thus, religion can be considered a specific form of spirituality, but spirituality is a broader concept.

We assessed spirituality and religion using the hope and faith facets of the World Health Organization Quality of Life Spirituality, Religiousness and Personal Beliefs WHOQOL-SRPB questionnaire (39). The WHOQOL-SRPB questionnaire does not tie spirituality to religion and questions are phrased in ways that apply to individuals with a wide range of religious and nonreligious beliefs. Each facet includes 4-items on a 5-point Likert scale. Computed scores were calculated as the sum of all items for each facet. Higher scores represent higher levels of hope and faith.

#### *6.3.3.6 Mental Health*

We used the WHO Self-Reporting Questionnaire (SRQ-20) to assess mental health. The SRQ-20 is a screening tool for mental disorders specifically designed for developing countries, consisting of 20 yes/no questions that add up to a maximum total score of 20 (40). Higher values are indicative of worse symptomology. For interpretation purposes, we reverse scored the final computed scores, so that higher values reflect better mental health.

### 6.3.4 Statistical Analysis

We used Structural Equation Modelling (SEM) techniques to examine factor-loadings patterns of studied domains and to assess intercorrelations between latent factors and observed variables. Under the Structural Equation Modeling (SEM) framework, we used first-order Confirmatory Factor Analysis (CFA) to investigate whether the established dimensionality and factor-loadings patterns for executive function and socioemotional scales (emotional support, faith, hope, happiness, life satisfaction, self-efficacy and meaning and purpose) fitted our sample population. For second-order factor structures (i.e., psychological wellbeing and spirituality and religion) we used hierarchical CFA to determine the degree to which factors loaded on their underlying sub-constructs.

Our final model **(Figure 6.1)** included the individual Likert-item responses from the NIH Scales assessing happiness, life satisfaction, meaning and purpose and self-efficacy as latent sub-domains of “psychological wellbeing”. Likert-item scale responses from the WHOQOL-SRPB hope and faith facets were modeled as latent sub-domains of “spirituality and religion”. Likert-item responses from the NIH Emotional Support Scale were used to model latent "emotional support". List Sorting Working Memory, Flanker Inhibitory Control and Attention, and DCCS Tests scores were modeled as latent "executive function". Mental health and IQ were modeled as observed variables using computed scores. Additionally, for comparison purposes, we tested a model in which the hope and faith facets were modeled together with happiness, life satisfaction, meaning and purpose and self-efficacy as additional subdomains of psychological well-being.

We assessed model fit using the root mean square error of approximation (RMSEA), Comparative Fit Index (CFI) and Tucker-Lewis index (TLI). A good model fit is indicated by RMSEA<0.08, CFI > 0.90 and TLI > 0.95.

Our analysis accounted for clustering of subjects within family and models were sex stratified. All analysis was conducted using MPLUS 8.0 using the Weighted Least Square Mean and Variance (WLSMV) estimator for categorical and ordinal responses using pairwise deletion of missing values (41).

## 6.4 Results

**Table 1** shows descriptive statistics. Computed scores for cognitive tests and socioemotional scales were similar across gender except for SRQ-20 scores which were higher in women. The majority of participants lived in rural areas (~70%).

Models in women and men showed adequate fit (RMSEA=0.04; CFI=0.95, TLI=0.95, and RMSEA=0.04, CFI=0.95, TLI=0.94, respectively). Models combining the hope and faith facets with psychological wellbeing components indicated a small decrease in goodness-of-fit indices (RMSEA=0.05, CFI=0.94, TLI=0.93 in women, and RMSEA=0.04, CFI=0.94 and TLI=0.93 in men). Thus, we decided to keep the model that differentiates spirituality and religion from psychological wellbeing.

First-order factor loadings for socioemotional scales are presented in **Supplemental Table 6.1**. Second-order CFA showed that the theorized subcomponents for spirituality and religion and psychological wellbeing highly loaded into their underlying constructs. Furthermore, we found that computed scores for List Sorting Working Memory, Flanker Inhibitory Control and Attention and DCCS tests loaded into executive function latent construct **(Table 6.2).**

Intercorrelation matrices between latent domains and observed variables in women and men are presented in **Tables 6.3 and 6.4**, respectively. All intercorrelations were positive. The strongest associations were observed between spirituality and religion and psychological well-being (r=0.68 and r=0.70 in women and men, respectively); and between executive function and IQ (r=0.63 and r=0.70 in women and men, respectively). Emotional support was weakly but positively associated with well-being and mental health (range r=0.32-0.35) in both genders. Also, we found that from all associations involving cognitive functions, those between executive function and spirituality and religion showed the highest correlations in women (r=38) and men (r=43). In both genders, executive function and IQ were weakly correlated with all other domains and showed no association with mental health.

## 6.5 Discussion

Our study investigated the interrelationships among psychological wellbeing, emotional support, spirituality and religion, mental health, IQ and executive function in a population of Guatemalan adults. Participants in our study face high levels of economic hardship and most were born into resource-limited environments that restricted growth and developmental potential. Thus, our study provides unique insights into the interplay of cognitive and socioemotional processes in contexts of adversity.

Our results derived from CFA support the construct validity of first order (i.e., emotional support, faith, hope, happiness, life satisfaction, self-efficacy, meaning and purpose and executive function), and second-order factor structures (i.e., psychological wellbeing and spirituality and religion). These findings indicate that the scales and tests used in this study measured the constructs adequately in this population.

Much debate has revolved around whether there is a meaningful differentiation between spirituality and religion from psychological wellbeing components. Our results were aligned with findings from a multicenter study in 15 countries indicated that although spirituality and religion are related to psychological wellbeing, they remain a distinctive domain, thus providing empirical evidence to support differentiation between the two constructs (42).

Our findings indicate strong correlations between psychological well-being, spirituality, and religion and between IQ and executive function. All other intercorrelations show small to medium effect sizes. Regarding the association between psychological wellbeing and spirituality and religion, our results are in line with previous research reporting similar results (43, 44). It has been suggested that the mechanism by which spirituality and religion influence psychological wellbeing involves certain psychosocial factors such as providing a sense of identity and social support and promoting an active and socially engaged lifestyle (15). Our findings on the association between emotional support (our measure of social support) and psychological wellbeing show weak correlations in women and men ($r=0.19$ and $r=0.32$, respectively, all $p<0.001$). However, our measure of social support was limited to emotional aspects and did not include components of instrumental support or social networks, which may be underestimating the associations.

The religious landscape in Guatemala may provide additional insights for the observed associations involving spirituality and religion. Pentecostal congregations rose in popularity in Guatemala during the late 1970s, turning it into one of the most protestant countries in Latin America (45). This is relevant because pentecostal churches are very supportive of their adherents providing them with various social services. The extent to which social support mediates the association between spirituality and psychological wellbeing remains to be further investigated.

We measured three core executive functions (working memory, inhibitory control, and cognitive flexibility) that facilitate higher-order executive function: problem-solving, reasoning and planning. In both genders, we found that executive function was strongly and positively correlated with measures of general intelligence (IQ). Our findings are consistent with previous studies indicating that performance on executive function tests, particularly on tasks assessing working memory capacity are associated with measures of intelligence (46, 47).

Also, we found that from all associations involving cognitive functions, those between executive function and spirituality and religion showed the highest correlations. Previous studies have reported associations between spiritual and religious involvement and better inhibitory control (48), and lower cognitive decline (49). Proposed mechanisms include the stimulation of higher cortical functions related to abstract thinking (16) and the promotion of a stimulating and socially engaged lifestyle that may help prevent cognitive decline (49).

It has been documented that people show better executive function capacities when they are happy, feel social supported and healthy (50). Our study findings show a weak association between executive function and psychological wellbeing in men ($r=0.23$, $p<0.001$), and no association in women. The mechanisms through which stronger executive functions positively influence various aspects of well-being (e.g., good relationships, health, and academic achievement) have been shown to involve the ability to inhibit automatic responses (i.e., self-control) and delay of gratification (51). These proposed mechanisms are derived from studies conducted in children and adolescents in developed countries (52-55). The underlying mechanisms influencing better outcomes among those with higher executive functions may operate differently depending upon the life stage (e.g., adolescents vs. adults) or living characteristics (e.g., poor vs. non-poor).

Our findings may have been limited by the crossectional nature of the data which does not allow for directionality or causality to be deduced. Despite these limitations, our study has several strengths. We applied cognitive and socio-emotional measures with good psychometric properties in a large sample of men and women living in rural areas of Guatemala and some in Guatemala City. Moreover, the use of structural equation modeling techniques allows examining interrelationships among factors and observed variables while accounting for measurement error.

Taken together this study provides important insights about the interplay of cognitive and socioemotional processes in populations living in poor resource settings of low-and middle-income countries. These findings provide an important step toward further elucidation of the different mechanisms that could promote human well-being in vulnerable populations.

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**Table 6. 1** Descriptive statistics (Mean ± SD, %) of demographic, cognitive and socioemotional measurements in study population by sex.

| | n | Women | n | Men |
|---|---|---|---|---|
| Age, y | 704 | 47.5 ± 4.3 | 564 | 47.4 ± 4.1 |
| Area of residence, % rural | 704 | 71.6 | 564 | 74.6 |
| ***Cognitive tests*** | | | | |
| List Sorting Working Memory score, (# correct out of 26) | 670 | 11.3 ± 3.8 | 541 | 12.7 ± 3.9 |
| Flanker Inhibitory Control and Attention score, (NIH score)[1] | 671 | 5.4 ± 1.1 | 542 | 5.8 ± 1.2 |
| DCCS score, (NIH score)[1] | 677 | 5.1 ± 1.9 | 546 | 5.4 ± 1.9 |
| Raven's Progressive Matrices score, (# correct out of 36) | 686 | 15.3 ± 4.9 | 537 | 17.8 ± 6.0 |
| ***Socioemotional scales*** | | | | |
| Lyubomirsky Happiness score (out of 5) | 700 | 4.0 ± 1.0 | 553 | 4.1 ± 0.9 |
| NIH Life Satisfaction score (out of 25) | 699 | 18.5 ± 3.5 | 553 | 18.9 ± 3.4 |
| NIH Meaning and Purpose score (out of 45) | 698 | 36.2 ± 4.1 | 552 | 37.2 ± 4.0 |
| NIH Self-efficacy score (out of 40) | 698 | 30.9 ± 7.1 | 552 | 31.4 ± 6.4 |
| NIH Emotional support score (out of 40) | 703 | 31.0 ± 9.3 | 559 | 32.5 ± 7.7 |
| WHOQOL-SRPB Hope facet score (out of 4) | 698 | 3.2 ± 0.8 | 552 | 3.3 ± 0.7 |
| WHOQOL-SRPB Faith facet score (out of 4) | 698 | 3.9 ± 0.7 | 552 | 3.9 ± 0.7 |
| SRQ-20 score (out of 20)[2] | 700 | 15.2 ± 4.0 | 558 | 17.7 ± 2.9 |

[1] Computed scores range from 0-10, but if the score is between 0 and 5, it indicates that the participant did not score high enough in accuracy (80 % correct or less) (25).

[2] Values were reverse scored so that higher values reflect better mental health.

Abbreviations: NIH National Institutes of Health; DCCS Dimensional Change Card Sort; WHOQoL SRPB World Health Organization Quality of Life Spirituality, Religiosity, and Personal Beliefs; SRQ-20 Self-Reported Questionnaire-20.

**Table 6. 2** Factor loadings for psychological wellbeing, spirituality, and religion, and executive function latent constructs.[1]

| | **Women** | **Men** |
|---|---|---|
| *Psychological Wellbeing scales* | | |
| Lyubomirsky Happiness | 0.73 | 0.69 |
| NIH Life Satisfaction | 0.86 | 0.86 |
| NIH Meaning and purpose | 0.83 | 0.83 |
| NIH Self-efficacy | 0.55 | 0.53 |
| *Spirituality and Religion*[2] | | |
| Faith | 0.79 | 0.73 |
| Hope | 0.91 | 0.88 |
| *Executive Function* | | |
| List sorting working memory test | 0.60 | 0.66 |
| Flanker Inhibitory control and attention test | 0.59 | 0.69 |
| DCCS[3] test | 0.82 | 0.70 |

1. All factor loadings are significant

2. Measured using the hope and faith facets of the World Health Organization Quality of Life Spirituality, Religiosity and Personal Beliefs (WHOQoL SRPB).

3. DCCS Dimensional Change Card Sort (DCCS)

**Table 6. 3** Correlation matrix of cognitive and socioemotional domains among adult women

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1. Psychological Wellbeing | - | | | | | |
| 2. Emotional Support | 0.34** | - | | | | |
| 3. Spirituality and Religion | 0.68** | 0.19** | - | | | |
| 4. Mental Health | 0.32** | 0.18** | 0.16** | - | | |
| 5. IQ | 0.15** | 0.09* | 0.27** | 0.08 | - | |
| 6. Executive Function | 0.08 | 0.15** | 0.38** | 0.08 | 0.63** | - |

Sample size is 704. *p<0.05; **p<0.001

**Table 6. 4** Correlation matrix of cognitive and socioemotional domains among adult men

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1. Psychological Wellbeing | - | | | | | |
| 2. Emotional Support | 0.35** | - | | | | |
| 3. Spirituality and Religion | 0.70** | 0.32** | - | | | |
| 4. Mental Health | 0.35** | 0.09* | 0.12* | - | | |
| 5. IQ | 0.25** | 0.11* | 0.32** | 0.09* | - | |
| 6. Executive Function | 0.23** | 0.22** | 0.43** | 0.08 | 0.70** | - |

Sample size is 564. *p<0.05; **p<0.001

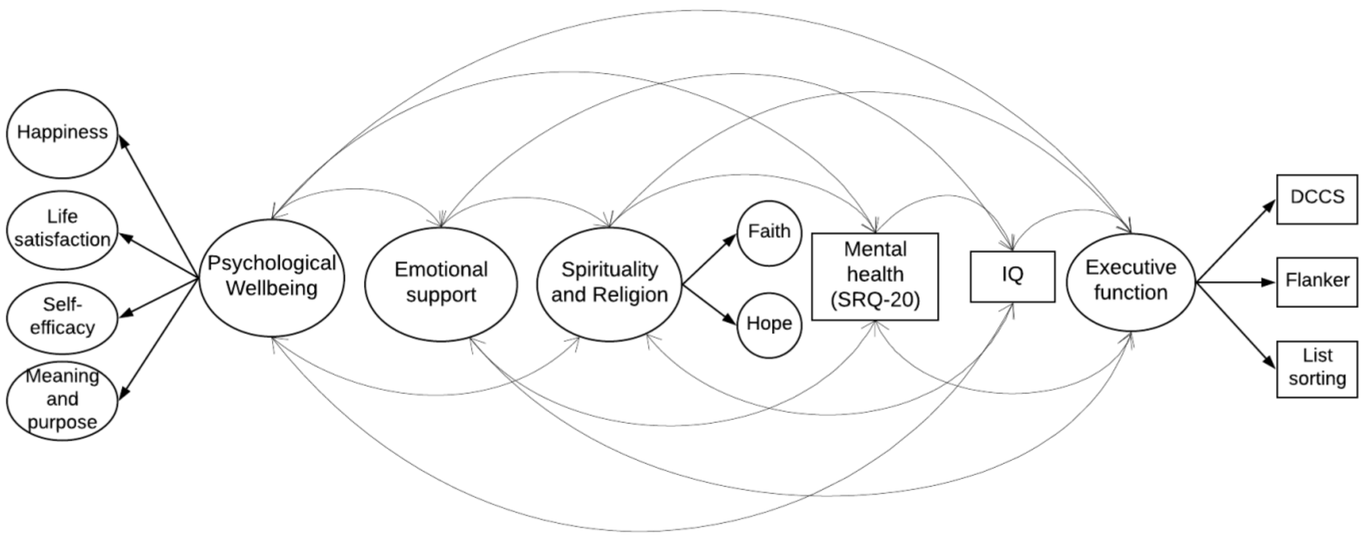


**Figure 6. 1** Hypothesized model

**Supplemental Table 6. 1** First-order factor loadings for socioemotional scales by gender.[1]

| | Women | Men |
|---|---|---|
| Happiness [2] | | |
| 1. How happy would you rate yourself? | 0.86 | 0.86 |
| 2. How happy would you rate yourself compared to most of your peers? | 0.89 | 0.77 |
| 3. Some people are generally very happy. They enjoy life regardless of what is going on, getting the most out of everything. To what extent does this characterization describe you. | 0.72 | 0.69 |
| 4. Some people are generally not very happy. Although they are not depressed, they never seem as happy as they might be. To what extent does this characterization describe you. | 0.40 | 0.47 |
| Life Satisfaction [3] | | |
| 1. My life is going well | 0.79 | 0.82 |
| 2. My life is just right | 0.79 | 0.76 |
| 3. I wish I had a different kind of life | 0.39 | 0.28 |
| 4. I have a good life | 0.83 | 0.87 |
| 5. I have what I want in life | 0.79 | 0.77 |
| Meaning and Purpose [4] | | |
| 1. I understand my life's meaning | 0.82 | 0.83 |
| 2. My life has a clear sense of purpose | 0.78 | 0.78 |
| 3. I have a good sense of what makes my life meaningful | 0.76 | 0.80 |
| 4. I have discovered a satisfying life purpose | 0.81 | 0.80 |
| 5. My life has no clear purpose | 0.28 | 0.41 |
| 6. I generally feel that what I do in my life is valuable and worthwhile | 0.81 | 0.86 |
| 7. I feel grateful for each day | 0.71 | 0.77 |
| 8. My daily life is full of things that are interesting to me | 0.83 | 0.80 |
| 9. There is not enough purpose in my life | 0.27 | 0.36 |
| Self-efficacy [5] | | |
| 1. I can manage to solve difficult problems if I try hard enough | 0.71 | 0.72 |
| 2. If someone opposes me, I can find the means and ways to get what I want | 0.70 | 0.59 |
| 3. It is easy for me to stick to my aims and accomplish my goals | 0.75 | 0.70 |
| 4. I am confident that I could deal efficiently with unexpected events | 0.78 | 0.71 |
| 5. Thanks to my talents and skills, I know how to handle unexpected situations | 0.82 | 0.76 |

| | | |
|---|---|---|
| 6. I can solve most problems if I try hard enough | 0.76 | 0.75 |
| 7. I stay calm when facing difficulties because I can handle them | 0.75 | 0.74 |
| 8. When I have a problem, I can find several ways to solve it | 0.78 | 0.75 |
| 9. If I am in trouble, I can think of a solution | 0.77 | 0.71 |
| 10. I can handle whatever comes my way | 0.73 | 0.66 |
| Emotional Support [6] | | |
| 1. I have someone who understands my problems | 0.76 | 0.77 |
| 2. I have someone who will listen to me when I need to talk | 0.84 | 0.80 |
| 3. I feel there are people I can talk to if I am upset | 0.89 | 0.79 |
| 4. I have someone to talk with when I have a bad day | 0.87 | 0.79 |
| 5. I have someone I trust to talk with about my problems | 0.87 | 0.87 |
| 6. I have someone I trust to talk with about my feelings | 0.87 | 0.82 |
| 7. I can get helpful advice from others when dealing with a problem | 0.83 | 0.76 |
| 8. I have someone to turn to for suggestions about how to deal with a problem | 0.76 | 0.70 |
| Hope [7] | | |
| 1. How hopeful do you feel? | 0.78 | 0.72 |
| 2. To what extent are you hopeful about your life? | 0.78 | 0.83 |
| 3. To what extent does being optimistic improve your quality of life? | 0.84 | 0.73 |
| 4. How able are you to remain optimistic in times of uncertainty? | 0.77 | 0.72 |
| Faith [8] | | |
| 1. To what extent does faith contribute to your well-being? | 0.88 | 0.81 |
| 2. To what extent does faith give you comfort in daily life? | 0.89 | 0.91 |
| 3. To what extent does faith contribute to your well-being? | 0.90 | 0.88 |
| 4. To what extent does faith give you strength in daily life? | 0.79 | 0.80 |

[1]All factor loadings are statistically significant p<0.01; [2] Lyubomirsky Subjective Happiness Scale;
[3] National Institutes of Health (NIH) Life Satisfaction Survey; [4] NIH Meaning and Purpose Survey;
[5] NIH Self-efficacy Survey; [6] NIH Emotional Support; [7] Hope facets of the World Health Organization Quality of Life Spirituality, Religiosity and Personal Beliefs (WHOQoL SRPB); [8] Faith facet of the WHOQoL SRPB.

# CHAPTER 7: Summary and Conclusions

The broad goal of this dissertation was to contribute to the understanding of the influence of early-life environments and post-natal linear growth on cognitive and socioemotional outcomes in adulthood. Specifically, this dissertation sought to: 1) examine the effect of exposure to nutritional supplementation in the first 1,000 days on executive function and socioemotional capacities at ages 40-57 years and investigate the mediating role of psychosocial stimulation and cognitive abilities on the association between early-life exposure to nutritional supplementation and adult socioemotional outcomes; 2) identify distinct trajectories of post-natal linear growth patterns from birth through age 7 years and examine their predictors and associations with executive function and socioemotional capacities at ages 40-57 years, and 3) determine the cross-sectional interrelationships between cognitive and socioemotional functioning in adulthood. The research was based in a prospective cohort of Guatemalan adults who, in early childhood, participated in a randomized food supplementation trial conducted between 1969-77 in four rural communities in eastern Guatemala.

## 7.1 Main Findings

### 7.1.1 Long-term effects of early-life nutritional supplementation on adult executive function and socioemotional capacities.

First, linear regression models with double-difference estimators were used to examine the influence of exposure to nutritional supplementation in the first 1,000 days on study outcomes. Results indicated that partial exposure to *atole* in the first 1,000 days (children that were either too young or too old to have been exposed to *atole* in the full first 1,000 days-window between 1969-77), was positively associated with measures of executive function. Specifically, pooled models showed a 1.24-point increment in List Sorting Working Memory scores (95% CI, 0.05, 2.42), and a 0.96-point increment in executive function latent construct (95% CI, 0.12, 1.79). In women, models showed a 0.93-point increment in Dimensional Change Card Sort scores (95% 0.19, 1.68). Also, results indicated that full exposure to *atole* in the first 1,000 days (from conception through maternal consumption during pregnancy and from birth to age 2 years through breastfeeding and the own child consumption), was positively associated with measures of socioemotional capacities. Specifically, pooled models indicated a 1.51-point increment in meaning and purpose scores (95% CI, 0.33, 2.69). Models in women showed a 2.9-point increment in self-efficacy scores (95% CI, 0.25, 5.55). No associations were observed in measures of subjective happiness and life satisfaction.

Second, using Structural Equation Modeling (SEM) techniques with double-difference estimators, the pathways between exposure to nutritional supplementation in the first 1,000 days and adult socioemotional functioning through psychosocial stimulation, executive function, and cognitive ability were examined. Results showed no evidence that psychosocial stimulation, executive function, or cognitive ability mediate the association between early-life nutritional supplementation and adult socioemotional functioning. Rather, standardized (STD) estimates showed significant direct and total associations between exposure to *atole* during the full first 1,000 days and adult socioemotional outcomes (STD $\beta$=0.44 95% CI, -0.02, 0.89, and STD $\beta$=0.47 95% CI, -0.13, 1.08, respectively). Furthermore, positive total associations were observed between full and partial exposure to *atole* in the first 1,000 days and cognitive ability (STD $\beta$=0.34 95% CI, -0.12, 0.80; $p$=0.05, and STD $\beta$=0.34, 95% CI, -0.07, 0.74; $p<0.05$), respectively. Another key finding was to find strong and positive direct associations between psychosocial stimulation and executive function (STD $\beta$=0.46, 95% CI, 0.20, 0.72), and between psychosocial stimulation and cognitive ability (STD $\beta$=0.57, 95% CI, 0.28, 0.85). Also, a total association was found between psychosocial stimulation and socioemotional functioning (STD $\beta$=0.23, 95% CI: -0.03, 0.50).

The hypothesis that children who were exposed to *atole* in the first 1,000 days would be more active and interested in exploring the environment, and as a result, would receive more stimulation from caregivers was tested. We found no evidence to support this hypothesis, suggesting that the effects of psychosocial stimulation on cognitive and socioemotional outcomes were independent of the nutritional intervention. In addition, the joint effects of exposure to *atole* in the full first 1,000 days and psychosocial stimulation on executive function, cognitive ability, and socioemotional outcomes were tested using interaction terms. No interaction was found between nutritional intervention and psychosocial stimulation.

7.1.2 Predictors of post-natal linear growth trajectories and associations with adult executive function and socioemotional capacities.

First, longitudinal trajectories of height-for-age-z scores (HAZ) from birth through age 7 years were identified using latent class growth analysis (LCGA). In LCGA, children who shared common longitudinal trajectories of observed HAZ scores were grouped into distinct latent classes. Results indicated three latent classes in females: high (34%), medium (50%) and low (16%); and three latent classes in males: high (32%), medium (50%) and low (18%), in the period between 0 to 84 months.

Identified linear growth trajectories in both genders showed similar (parallel) slopes that were primarily distinguished as a matter of severity of linear growth faltering at birth (intercepts). The early differentiation of trajectories at birth has important public health implications, suggesting that prenatal factors play a crucial role in establishing life course linear growth trajectories (see section 7.2 for discussion).

Second, predictors of high latent class membership, in other words of higher likelihood of belonging to the high-HAZ linear growth trajectory, were analyzed using multinomial logistic regression models. Results from multinomial logistic regression models with the low-HAZ class as the reference category showed that maternal height was positively associated with likelihood of belonging to the high and medium HAZ trajectory relative to the low HAZ trajectory among females (Relative Risk Ratio (RRR)= 1.21 95% CI: 1.14, 1.29, and RRR=1.10 95% CI: 1.05, 1.16) and males (RRR=1.20 95% CI: 1.14, 1.27, and RRR=1.11 95% CI: 1.05, 1.16), respectively. Also, belonging to the wealthiest versus the poorest socioeconomic tertile was associated with membership to the high-HAZ linear growth trajectory relative to the low-HAZ linear growth trajectory in females (RRR = 2.88 95% CI: 1.41, 5.90).

To examine the role of exposure to nutritional supplementation in the first 1,000 days on linear growth, we identified HAZ linear growth trajectories in a subsample of the study population (children 36 to 84 months of age). Identified trajectories in children 36 to 84 months showed similar parameters (intercept and slope) to those identified in children 0 to 84 months, and included two latent classes in females: high (58%), low (42%), and three classes in males: high (25%), medium (51%), and low (25%). Results indicated that exposure to *atole* in the first 1,000 days was associated with a higher likelihood of belonging to the high-HAZ linear growth trajectory relative to the low-HAZ linear growth trajectory among females (RRR= 2.9 95% CI: 1.26, 7.11). In males, associations were also positive but did not reach statistical significance. These results are consistent with previous analyses conducted in this population, indicating that the nutritional intervention improved linear growth in both sexes during the first 36 months (1). Additionally, in both sexes, maternal height was also positively associated with high HAZ class membership in females (RRR=1.17 95% CI, 1.10, 1.23), and males (RRR=1.23 95% CI, 1.13, 1.34).

During the nutritional trial, length was measured every three months from birth to age 24 months, every six months from 24 to 48 months, and every year from 48 to 84 months. A sensitivity analysis was conducted to account for the variability in the number of data points and their spacing, in which the identification of linear growth trajectories was restricted to children with available HAZ at birth, 48 months, and at least one HAZ between birth and 48 months. Results from the sensitivity analysis showed that linear growth trajectories remained similar to those derived using other age windows.

Third, associations between linear growth trajectories in the period between 0 to 84 months, and adult executive function and socioemotional capacities were examined using linear regression models. Models controlled for the nutritional intervention, maternal and childhood socioeconomic characteristics. Results showed a gradient of positive associations between HAZ linear growth trajectories and all measures of cognitive ability (i.e., non-verbal fluid intelligence, working memory, inhibitory control, and cognitive flexibility) at ages 40 to 57 years, but only among men. Specifically, high-vs. low-HAZ trajectory was positively associated with Raven's Progressive Matrices (β=4.10, 95% CI: 2.49, 5.72), List Sorting working memory (β=1.73, 95% CI: 0.50, 2.96), Flanker inhibitory control and attention (β=0.65, 95% CI: 0.30, 0.98), and DCCS test scores (β=1.21, 95% CI: 0.67, 1.75). Associations between medium vs. low-linear growth trajectories and cognitive outcomes were of less magnitude but remained significant. Models examining associations between growth trajectories and adult socioemotional outcomes showed no major differences by sex. Pooled results indicated that membership to the high linear growth trajectory (vs the low), was associated with higher scores on scales assessing happiness and meaning and purpose.

A sensitivity analysis was conducted to examine the consistency of the study findings with those using other methodologies to assess early-life linear growth (i.e., conditional growth variables and HAZ at 24 months). Overall, results from sensitivity analysis were consistent with those derived using LCGA (see section 7.2 for further discussion).

Last, a mediation analysis was conducted to investigate the role of schooling in the association between post-natal linear growth trajectories and cognitive scores found in men. In this prospective cohort, men completed, on average, one more year of schooling than women. Results indicated that the magnitude of the indirect effect through completed grades of schooling corresponded to 30% of the total effect of high latent class (vs. low class) on Raven's Progressive Matrices scores (Total effect Standardized (STD) $\beta$=0.64 95% CI, 0.29, 0.98; indirect effect through schooling STD $\beta$=0.19 95% CI, 0.02, 0.36), and 35% of the total effect of high latent class (vs. low class) on List Sorting Working Memory scores (Total effect STD $\beta$=0.45 95% CI, 0.02, 0.89, indirect effect through schooling STD $\beta$=0.16 95% CI, 0.02, 0.29). Similar associations but in lesser magnitude were observed between medium latent class (vs. low) and computed scores on Raven's Progressive Matrices and List Sorting Working Memory through completed grades of schooling.

7.1.3 Interrelationships between cognitive and socioemotional functioning in adulthood.

SEM techniques were used to assess interrelationships between cognitive and socioemotional factors in adulthood. Studied domains included measures of executive function, non-verbal fluid intelligence, happiness, life satisfaction, meaning and purpose, and self-efficacy. This analysis also incorporated other factors known to be associated with both cognitive and socioemotional capacities, namely measures of mental health, social support, spirituality, and religion. First-order Confirmatory Factor Analysis (CFA) was used to investigate whether the established dimensionality and factor-loadings patterns for executive function and socioemotional scales assessing emotional support, faith, hope, happiness, life satisfaction, self-efficacy and meaning, and purpose, fitted our sample population. For second-order factor structures (i.e., psychological wellbeing and spirituality and religion), hierarchical CFA was used to determine the degree to which factors loaded on their underlying sub-constructs. A "psychological wellbeing" domain was proposed to include subdomains of happiness, life satisfaction, meaning and purpose, and self-efficacy. The domain for "spirituality and religion" was proposed to include hope and faith facets. Results showed that the theorized subcomponents for spirituality and religion and psychological wellbeing highly loaded onto their underlying constructs.

All intercorrelations between study domains were positive. In women, the strongest associations were observed between spirituality and religion and psychological wellbeing ($r=0.68$, $p<0.001$) and between executive function and IQ ($r=0.63$, $p<0.001$). Executive function and IQ were weakly correlated with all other domains and showed no association with mental health. The correlation matrix in men showed somewhat similar results. The strongest association was observed between spirituality and religion and psychological wellbeing ($r=0.70$, p<0.001). Also, executive function and IQ were strongly correlated with each other (r=0.70, p<0.001), moderately correlated with emotional support, and weakly correlated with all other domains.

## 7.2 Discussion

It is well accepted that nutritional deficits in the first 1,000 days have short, medium, and long-term effects on cognitive abilities. However, the socioemotional consequences of early-life nutritional deficits are less well understood. Furthermore, recent academic debate has suggested that cognitive development may also respond to interventions post–1000 days (2), and that linear growth retardation and stunting should not be the focus of interventions that look to improve child mental development because it is unlikely that a causal association exist between these two (3, 4). This has been influenced by:

First, the implausibility, based on current understandings, of the proposed pathways linking stunting to developmental delays. For instance, stunting is thought to be associated with reduced motor activity, limiting the child's ability to explore the environment and receive psychosocial stimulation, and thus reducing opportunities for the development of socioemotional and cognitive capacities (5). However, studies suggest that the attainment of gross motor skills is largely independent of variations in linear growth (6). Moreover, there is little evidence for a positive association between gross motor and mental development (7). The second potential mechanism implies that short stature children lowers caregivers' expectations about children's developmental potential, potentially reducing opportunities for psychosocial stimulation and learning opportunities (8). However, it has been acknowledged that this mechanism is not likely to be meaningful in populations like Guatemala, in which the majority of children suffer from some degree of linear growth faltering (3). Second, findings from path analysis studies using data from several cohorts in LMICs suggesting that predictors of cognitive development and height-for-age scores are only partially shared (9-11). Third, an emerging body of evidence showing that post-natal linear growth throughout the ages of 9 to 12 years is weakly associated with language and math achievement at age 12 years (12), and measures of cognitive and academic scores at ages 9 to 12 years (13).

This dissertation addresses current gaps in the literature and adds to the current academic debate with evidence suggesting that: 1) early-childhood nutrition interventions have long-lasting effects on socioemotional capacities; 2) benefits of improved nutrition on the development of executive function skills may extend the first 1,000 days-window; 3) psychosocial stimulation in early childhood strongly predicts executive function and cognitive ability at ages 40 to 57 years, and; 4) linear growth trajectories throughout childhood positively associate with measures of executive function and non-verbal fluid intelligence at ages 40-57 years, and these associations are partially mediated by completed years of schooling. A detailed discussion of the study findings addressing each of these claims is provided as follows:

First, significant associations were found between partial exposure to *atole* in the first 1,000 days and measures of executive function in adulthood. An important consideration is that the majority of children that were partially exposed to *atole* in the first 1,000 days consisted of children that were too old to have been exposed to *atole* during the full 1,000 days window. This is relevant because although the neural connections that support the development of higher-order cognitive functions peak at 12 months of age, it is well established that the development of executive function skills extend well beyond the first 1,000 days window. For instance, studies show that the development of working memory capacity starts in the first year of life and continues at least into adolescence with alternating periods of rapid and more stable growth (14). The first spur occurs between the ages of 2 and 8 years (15-18).

The development of neurons in the brain begin during gestation and continue throughout infancy. Neurons connect to each other via synapses forming neural circuits. It is well studied that following a period of neuron and synapsis overproduction, the brain undergoes a process of systematic pruning in which neurons that fail to make a connection are removed through apoptosis (19), and the neural connections that are left increase in speed and efficiency through myelination. Pruning and myelination are more prevalent in early childhood but continue throughout life (20, 21). For instance, the prefrontal cortex, the area of the brain responsible for the acquisition of executive function skills becomes fully myelinated around early adulthood (22). Thus, findings from this dissertation suggest that the benefits of improved nutrition on the development of executive function skills extend the first 1,000 days-window and may be involved with pruning and myelination processes that occur later in development.

Regarding the associations found between full exposure to *atole* in the first 1,000 days and adult socioemotional capacities, these results are consistent with two previous studies conducted in this cohort, documenting better behavioral outcomes at ages 6 to 8 years among children that received higher intakes of nutritional supplementation during infancy (23, 24). Our results, together with those from Barret, Radke-Yarrow and Klein (1982), suggest that nutrition interventions have long-lasting effects on socioemotional capacities and that benefits acquired in childhood remain throughout adulthood.

A compelling biological explanation for the observed association between nutritional supplementation on cognitive and socioemotional outcomes could be attributed to the role of stress. It is well documented that during critical periods of brain development, prolonged exposure to stress hormones can impair the development of neural connections, particularly in regions of the brain dedicated to higher-order skills, causing life-long problems in learning and behavior (25). Undernutrition exposes the body to stress hormones, specifically cortisol (26, 27). Moreover, children living in poverty are usually more exposed to multiple stressors (e, g., domestic or community violence, poor social support, unresponsive parenting). Thus, findings from this dissertation suggest that early-life exposure to enhanced nutrition may have the potential to mitigate the disruptive effects of multiple stressors during critical windows of brain formation. The specific pathways through which this could operate remain to be understood.

Another biological explanation for the observed associations between nutritional supplementation on cognitive and socioemotional outcomes involves metabolic pathways. For instance, it is well accepted that development requires energy. Studies show that in resting state at least 20% of the body's glucose is used by the infant’s brain. Thus, low levels of energy in the first few years of life may have the potential to reduce the amount of brain activity and development (8).

An important finding in this dissertation was to find strong and positive associations between psychosocial stimulation and executive function, cognitive ability, and socioemotional functioning. Results indicated that associations between psychosocial stimulation and cognitive abilities were stronger than those between nutritional supplementation and cognitive abilities. These findings are in line with previous meta-analysis showing that nutritional interventions have approximately one third of the effect on neurobehavioral development compared with stimulation interventions (4, 8). Findings from this dissertation, together with studies in Jamaica (28, 29) and Pakistan (30), suggest that early-life investments in psychosocial stimulation and nutrition may produce greater long-term benefits on cognitive functioning than nutritional supplementation alone.

Second, linear growth trajectories derived between 0 to 84 months show similar (parallel) slopes that are primarily distinguished as a matter of severity of linear growth faltering at birth (intercepts). Early differentiation of trajectories suggests that prenatal factors play a crucial role in stablishing life course linear growth. Assessed predictors of linear growth trajectories indicated a combination of genetic (i.e., maternal height) and environmental factors (i.e., socioeconomic status and exposure to nutritional supplementation). The influence of maternal height in offspring's linear growth is thought to reflect a complex interplay between genetic characteristics, and intergenerational effects of the environment in which the mother grew up and developed (31). Short women (<145 cm) are also at higher risk of having small for gestational age (SGA) children, who, in turn, are more likely to suffer from stunted growth in early childhood (32, 33). The proposed biological mechanisms linking short maternal stature to SGA include low uterine volume and small pelvic size (33). Regarding household socioeconomic status and nutritional exposures, it is well documented that determinants of growth retardation are rooted in poverty and result from a combination of inadequate feeding practices, which include lack of exclusive breastfeeding, poor infant and young child feeding practices, infections, and inadequate childcare practices (34). Moreover, results from this dissertation showed that the nutritional intervention improved linear growth in the first 36 months. This finding is consistent with previous studies conducted in this population (1), and confirm the well-known association between nutrition and linear growth.

Findings from this dissertation revealed modifiable and non-modifiable risk factors for early-life growth faltering. Modifiable risk factors included feeding practices and characteristics of the environment. Household socioeconomic status (SES) is a widely recognized determinant of growth faltering. Analysis of Demographic and Health Surveys in 72 low-income countries show that differences in stunting rates between poor and rich households are small in the first 5 months of life, becoming more pronounced thereafter (35). This period coincides with an age in which children are more directly exposed to the environment and living conditions. For early childhood interventions to have a positive impact on child development and growth, behavioral change of caregivers needs to be adequately addressed. Researchers and intervention programs have moved toward changing behavior in psychosocial stimulation (through play and talk), feeding (quantity and quality of foods), and hygiene practices (handwashing) rather than tackling one problem alone (8). However, more focalized resources, local and governmental support, are required for these programs to yield better outcomes and be effective.

Also, findings from this dissertation showed a gradient of positive associations between HAZ linear growth trajectories through age 7 years, and scores on measures of cognitive ability in men. Positive, significant, and strong associations were found between high-HAZ linear growth trajectory versus low-HAZ linear growth trajectory and measures of non-verbal fluid intelligence ($\beta$=4.1), working memory capacity ($\beta$=1.7), inhibitory control ($\beta$=0.65) and cognitive flexibility ($\beta$=1.21) in men.

A key question to address given the similar (parallel) slopes found between linear growth trajectories was to examine whether associations between trajectories and study outcomes differ between linear growth in early versus later childhood. A sensitivity analysis was conducted to address this question, using conditional growth variables, and separately, HAZ at or close to 24 months as predictors of adult cognitive and socioemotional functioning. Results using both approaches revealed that early rather than later, linear growth is more strongly and significantly associated with cognitive and socioemotional outcomes. Results from sensitivity analysis were also consistent with findings derived using LCGA techniques, which indicated that associations between trajectories and outcomes of interest were primarily distinguished as a matter of severity of linear growth faltering at birth. Moreover, all used analytical approaches testing whether linear growth trajectories, conditional growth variables, or HAZ at 24 months predicted cognitive and socioemotional outcomes showed positive associations in men but not in women, particularly for cognitive outcomes.

Findings from this dissertation are consistent with many other studies showing positive associations between linear growth in early childhood and measures of adult cognitive ability. These findings also contradict other studies using similar methodologies. For instance, Kowalski et al. (2018) using data from Ethiopia, Peru, India, and Vietnam documented that post-natal linear growth between ages 1 and 12 years was weakly associated with scores on tests of language and math achievement at age 12 years (12). Prado et al. (2017) showed that childhood linear growth from birth to age 9 years was weakly associated with cognitive and academic scores at ages 9 to 12 years (13).

Moreover, this dissertation documented that completed grades of schooling partially mediates the associations between linear growth trajectories and measures of working memory capacity and non-verbal fluid intelligence in men. Adequate linear growth is an indicator of child health and a well-known determinant of childhood morbidity and mortality (36). It is possible that children in the high-HAZ trajectory may have also been healthier than those in the low-HAZ trajectory. Healthy children are less likely to miss school and as a result, have more opportunities to receive stimulation from teachers and peers. Studies suggest that school environments may provide unique opportunities for children to improve and exercise their executive function skills, particularly for those coming from less supportive home environments (37, 38). Furthermore, these findings are consistent with previous studies suggesting that children who complete more years of formal schooling score higher on measures of executive function (39, 40).

Third, it is well established that developmental domains (physical, cognitive, language and socioemotional) develop in mutual coordination to support the development of each other (41). We examined the interrelationships between cognitive and socioemotional factors in adulthood. Results showed strong correlations between measures of non-verbal fluid intelligence (IQ), and executive function. These results are in line with previous studies indicating that performance on executive function tests, particularly on tasks assessing working memory capacity are associated with measures of intelligence (42, 43). However, a weak association between executive function and psychological wellbeing was found in men ($r=0.23$, $p<0.001$), and no association was found in women.

The mechanisms through which stronger executive function positively influence different aspects of wellbeing (e.g., good relationships, health, and academic achievement) have been shown to involve the ability to inhibit automatic responses (i.e., self-control) and delay of gratification (44). These proposed mechanisms are derived from studies conducted in children and adolescents in developed countries (45-48). Findings from this dissertation, specifically the weak association found between executive and socioemotional functioning, suggest that the underlying mechanisms influencing better outcomes among those with higher executive functions may operate differently depending upon the life stage or living characteristics.

### 7.3 Strengths and Limitations

A major strength of this dissertation was the use of rich and extensive longitudinal data collected over 50 years. In addition, the methods used for assessing the effects of nutritional supplementation on cognitive and socioemotional outcomes used an experimental design and were well suited for evaluating the intervention, allowing for causal inferences to be more plausible. The use of double difference estimators allowed to isolate the effect of exposure to *atole* in the first 1,000 days, relative to the control group *fresco* controlling for village-level differences or other period or cohort effects. This was relevant because treatment assignment was allocated at the village level, and with only two villages per treatment, potential baseline differences between treatment groups may not have been adequately addressed by randomization. Another analytical strength of this dissertation was the use of structural equation modeling techniques. Because latent variables extract the common variance from multiple measures, specific variance and measurement error are largely eliminated, resulting in increased statistical power and more accurate parameter estimates. Moreover, structural equation modeling allows to adequately explore associations by integrating a measurement model that links observed variables to unobserved latent variables through confirmatory factor analysis (CFA), and a structural model that links the latent variables to each other via a system of simultaneous equations (49).

This dissertation also has limitations. The main limitation is that additional and comparable measures of executive function and socioemotional capacities were not available at earlier points in time, for instance, during childhood or adolescence. This can be problematic given the need to ensure that individual differences of such characteristics remained stable through time. From a developmental standpoint, ensuring stability through time implies that measures collected in adulthood can adequately reflect the past of such characteristics. Therefore, the conclusions drawn in this dissertation about the influences of early life nutrition and psychosocial stimulation on executive function and socioemotional capacities are valid to the extent that individual differences on executive function and socioemotional capacities had remained stable over time, in other words, that participants had maintained their order relative to one another in the cohort.

A potential threat to the validity of our results is attrition. Using a conservative definition of attrition by which deaths are regarded as cases lost to follow up, attrition in the 2017-19 follow-up wave was 47%. If deaths are accounted as having been traced, attrition was 37%. These rates are similar to those reported in previous waves (50, 51), were lost-to-follow-up was not differential in terms of random assignment to the nutritional intervention.

Regarding the generalizability of our results, this study was conducted using data from one developing country (i.e., Guatemala). Although many socioeconomic and cultural differences exist among developing countries, there are also many similarities that developing countries experience in the underlying determinants that contribute to developmental delays. Thus, findings from this dissertation can be applicable to many other LMICs settings under similar contexts.

## 7.3 Future directions

The body of evidence indicating that the origins of adult health, social and emotional wellbeing are established in early childhood, have generated political momentum to address childhood development and its long-term consequences. Moreover, the United Nations has adopted Sustainable Development Goals for children's health and development (52). This requires standardized instruments that allow us to measure and monitor developmental domains across populations adequately.

The Developmental score (D-score) metric has recently been developed using existing data from 16 longitudinal studies and 11 countries (53). A validated version of the D-score could be used to convert data from different settings to a common metric and to construct new instruments to assess child development for global use. Future efforts should be made to also develop and harmonize socioemotional measures that could be applied throughout childhood across different social and cultural contexts. Moreover, while progress has been made in the design and validation of instruments for cognitive development, the consensus about the constructs and measurement approaches for social and emotional development is lacking. As a first step, it is important that studies in LMICs incorporate existing measures of socioemotional development in early childhood. For instance, the Griffiths and the Bayley Scales include items that capture children's social interactions and expression of emotional states and interactive behaviors. However, a caveat is that these measures would first need to be validated for cultural appropriateness.

Measures of secure attachment are widely applied in developmental psychology research. Secure attachment is considered the most important socioemotional capability acquired in early childhood (54). Although measures developed to capture secure attachment such as “the strange situation” are not field-friendly, efforts should be made to collect these measures. An increased focus on the social and emotional aspects of child development could spark increased interest in mobilizing resources to develop and harmonizing socioemotional measures with good psychometric properties that can be applied throughout childhood across different social and cultural contexts.

Second, studies from animal and human populations have shown that the timing and severity of nutritional deficits have differential effects on brain development. Findings from this dissertation suggests the need to consider the timing of nutritional exposures in the development of executive function skills. This could be accomplished with the use of magnetic resonance imaging (MRI) technologies. For instance, MRI studies could help identify if changes in regions of the brain involved in working memory capacity during periods of early-brain development vs. periods of rapid growth are attributable to nutritional exposures. Also, and perhaps more critical to the current debate, studies using MRI technologies could help identify if linear growth is a proxy (or not) for better brain development.

Lastly, the evidence is accumulating that nutritional supplementation and psychosocial stimulation together may result in greater benefits for child development than either intervention alone (55). Findings from this dissertation together with several other studies in LMICs, indicate the need to identify evidence-based and comprehensive intervention packages that integrate psychosocial stimulation and nutritional components (56).

A successful example of integrated interventions includes the Pakistan Early Child Development Scale-Up Trial (30). This study investigated the feasibility and effectiveness of a combined intervention package that included counseling in nutrition and multiple micronutrient powders and psychosocial stimulation components. The intervention was delivered monthly and involved group sessions and home visits to rural households with children under two years, by front line health workers as part of the government health system in Sindh, Pakistan. Results showed independent benefits of psychosocial stimulation and nutrition components on cognitive, language, and motor development (30). However, even though no added benefits of combining the two interventions were observed on child developmental outcomes, there were no adverse effects of combining both approaches either. Furthermore, the integration of nutritional and psychosocial stimulation components resulted in efficient use of resources and saved program costs.

Both nutrition and stimulation interventions in LMICs are labor-intensive and require a delivery format. Stimulation interventions in LMICs are based on providing children with play activities and materials, along with adult conversation (57). Stimulation interventions require the use of curriculum and trained personnel who usually require supervision. Nutrition interventions operate much like stimulation interventions. These interventions are delivered to the child's caregivers. Information about adequate breastfeeding and complementary feeding practices starting at 6 months of age are transmitted, along with recipes and, in some cases, cooking demonstrations (58). Some also incorporate hygiene messages such as hand washing and storing leftover food if refrigeration is not available. Three common delivery formats are commonly implemented: home visits, group sessions, and clinic appointments, all of which present different challenges and opportunities. In a systematic review and meta-analysis, Aboud & Yousafzai (2015) identified that the most promising model for early-childhood programs is group sessions along with some home visits (8). This model is less labor-intensive than home visits, encourages peer support, and has the potential to modify caregiver’s behavior for child-rearing.

## 7.4 References

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