NEUROCOGNITIVE CHANGES IN CAMBODIAN INFANTS FOLLOWING THIAMINE SUPPLEMENTATION: AN ANALYSIS OF CONTRIBUTING FACTORS

by

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A THESIS

Presented to the Department of Psychology
and the Robert D. Clark Honors College
in partial fulfillment of the requirements for the degree of
Bachelor of Science

May 2025

An Abstract of the Thesis of

Tess Conway for the degree of Bachelor of Science
in the Department of Psychology to be taken June 2025

Title: Neurocognitive Changes in Cambodian Infants Following Thiamine Supplementation

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This study investigated the long-term effects of maternal thiamine supplementation on infant neurodevelopment, with a specific focus on understanding the decline in language scores observed between 6 and 12 months of age. Building upon data from a randomized controlled trial in Cambodia (Whitfield et al., 2019), infants were assessed using the Mullen Scales of Early Learning (MSEL) at 2 weeks, 24 weeks (endline), and 52 weeks. While scores in motor and visual reception domains generally improved, significant declines were noted in expressive and receptive language subscales following the cessation of maternal supplementation at 6 months. Autoregressive models tested whether demographic and anthropometric factors—including maternal milk thiamine levels, parental education, household income, infant sex, and stunting—predicted developmental change. Although early maternal milk thiamine levels predicted improvements in fine motor and language scores during supplementation, no predictor consistently accounted for post-supplementation declines. The findings suggest that discontinuing thiamine supplementation at 6 months, coinciding with increased infant thiamine needs and the transition to complementary feeding, may have contributed to the observed language setbacks. These results underscore the importance of sustained nutritional support during critical developmental windows and highlight the need for continued research incorporating dietary data to guide targeted interventions in low-resource settings.

Acknowledgements

This project would not have been possible without the dedication of my Primary Thesis Advisor, Dr. Jeffrey Measelle, thank you for your support and commitment to this project. I would not have been able to accomplish this thesis without your guidance, and for that I am so grateful. I would also like to thank my CHC advisor, Dr. Dare Baldwin, whose work inspires me immensely, I am very thankful for your time, and I appreciate your contributions to this project. I am deeply thankful for the opportunity to contribute to the Cambodia Project, and to Dr. Kyly Whitfield for laying the foundation of the Cambodia Project. Your work is invaluable, and this project has meant so much to so many individuals.

To all of my professors, and peers at the University of Oregon, I am thankful for all of the experiences, knowledge, and encouragement I have gained through my time here. To my roommates and friends who have made Eugene and the University of Oregon home, I am forever grateful for all of your encouragement during these important years. You all have been the kindest listeners, and best study buddies I could ever ask for during long hours spent writing at the library.

Thank you to my family, you guys are the best. And of course, I am thankful to my mom. She is my world.

Table of Contents

Introduction 7

Literature Review 7

Hypotheses 21

Methods 23

Ethical Attainment 23

Participants 23

Data Collection Procedures 23

Measures 24

Results 27

Sample and Descriptive Statistics 28

Correlational Analyses 30

Change in MSEL Scores 32

Regression Models for Endline Outcomes 33

Regression Models for 12-Month Outcomes 36

Discussion 40

Bibliography 51

List of Figures

Figure 1: Developmental trajectories of MSEL change by thiamine dosage levels. 27

List of Tables

TABLE 1. Sample Characteristics and Descriptive Statistics 29

Table 2a. Intercorrelations Among Predictors 31

Table 2b. Intercorrelations Between Predictors and Infant MSEL Scores as 2- 24- and 52-weeks 32

Table 3. Sample Changes in Standardized MSEL Scores Between 6- and 12-months and the Proportion of Infants Shown a Decrease vs. Increase 33

Table 5. Regression Models Predicting 12-Month MSEL Scores While Controlling for Endline MSEL Scores 37

Introduction

Literature Review

This study explores the critical issue of malnutrition, specifically, deficiencies in the micronutrient vitamin B1 or thiamine, and its impact on infant neurodevelopment in Southeast Asia. The literature review starts by distinguishing between macronutrient and micronutrient undernutrition and then, more specifically, it focuses on thiamine deficiencies. The essential role of thiamine in metabolic and neurological processes is reviewed, especially as it might affect infants. Severe thiamine deficiency can lead to conditions like Beriberi and Wernicke-Korsakoff syndrome, with significant consequences for cognitive and motor functioning. In Southeast Asia, particularly Cambodia, thiamine deficiency is prevalent due to rice-based diets that lack dietary diversity, contributing to infant mortality and developmental delays. A randomized controlled trial in Cambodia, which serves as the basis for the present study, examined the effects of maternal thiamine supplementation on infant cognitive, motor, and language skills using the Mullens Scales of Early Learning (MSEL). The study found that higher thiamine intake across the first six months of life was linked to improved infant language development at 24 weeks postnatal, though these benefits diminished by 52 weeks, raising specific questions about which infants showed a decline in cognitive gains, and questions about long-term supplementation strategies more generally. Using a panel of demographic characteristics from this parent study, the present study sought to identify factors that might account for changes in infants' neurocognitive development following thiamine supplementation both across the period of the intervention and through 12 months postpartum.

Malnutrition

Nutrients are defined as "the essential components required to sustain life" (Espinosa-Salas et al. 20). Without nutrients, the condition of malnutrition occurs, which is characterized by an imbalance between the nutrients your body needs to function and the nutrients it receives (World Health Organization, 2006). There are two forms of malnutrition: macronutrient undernutrition occurs when your body does not receive the necessary amount of protein, carbohydrates, and fats it needs to function. Micronutrient undernutrition occurs when your body does not regularly receive vital vitamins and minerals. Macronutrient and micronutrient undernutrition occurs in developed countries in poorer areas, and in developing countries where there is limited accessibility to dietary diversity or food resources in general (World Health Organization, 2006). The causes of malnutrition surround limited financial resources, limited access to nutritious food, and extra need for calories during pregnancy, breastfeeding, or childhood development.

Children require greater nutritional intake than adults due to their rapidly growing brains and bodies (Cusick, 2016, UNICEF), with economically disadvantaged children at higher risk of undernutrition (Hong et al, 2006). The consequences of undernutrition appear physically in symptoms such as thin arms and legs with edema in the belly and face, stunted growth, low body weight, depleted fat and muscle, and appear cognitively through stunted intellectual development (WHO, n.d). Stunting and wasting are two common forms of undernutrition. Stunting is characterized by small stature "height-for-age <-2 SD of the WHO Child growth standards median" (WHO, n.d), as well as delayed mental development. Women who were stunted experience greater risk during pregnancy, deliverance and can cause low birthweight contributing to a cycle of malnutrition (WHO). Wasting is characterized by "weight-for-height

<-2 SD of the WHO Child growth standards median" caused by acute malnutrition and can be fatal (WHO). Both stunting and wasting measures are reflective of a child's growth being restricted by poor environmental conditions (Black et al, 2013). Environmental conditions throughout the world contribute to a high prevalence of micronutrient deficiencies, affecting over 2 billion people, especially pregnant women and children (Espinosa-salas et al, 2023).

Micronutrients and Malnutrition

Similar to macronutrient undernutrition, long term micronutrient deficiency can cause serious impacts on the brain and body (Fattal-Valevski et al, 2005). Micronutrients are needed in small amounts to assist in biochemical processes in the body by supporting metabolic function, and physiological processes such as enzymatic reactions (Espinosa-Salas, 2023). There are two classifications of micronutrients, vitamins and minerals, both of which are essential in our diet due to our body's inability to synthesize them endogenously. Vitamins can either be fat-soluble (stored in the body in adipose tissue) or water soluble (washed out through the body). Due to their low incidence in many diets, most vitamins have recommended supplementation or are accessible through fortified foods (Lykstad & Sandep, 2023. WHO, 2006.)

Fat Soluble vitamins are absorbed and can be stored in the body in adipose tissue. Some examples of fat-soluble vitamins are vitamin A, and vitamin D. Vitamin A, retinol is important for vision, and "can be found in animal products, including liver, kidney, oils, dairy products, and eggs" (Espinosa-Salas et al, 2023). Recommended daily allowance of vitamin A for adults is 700/900 micrograms a day for women/men, and 300-900 mg for children. This number changes to 770 mg for pregnant women, and 1300 mg for women who are lactating (Espinosa-Salas 2023, Whitfield et al 2019, NIH 2024). Vitamin D is absorbed from fatty fish, or synthesized through sunlight exposure. The nutritional recommendation relates to age, location, sun

exposure, and since there is a low incidence of vitamin D in most foods' supplementation is recommended. As you can see, storable micronutrients are necessary in the daily diet, increasing largely for pregnant women, lactating women and children due to the constraints of growth.

Water soluble vitamins are absorbed into the bloodstream and used throughout the body, making them hard to store. Meeting the adequate intake for water soluble vitamins is vital due to their constant usage and lack of storage in the body. Without adequate intake, the body will become deficient in most of these vitamins (Lykstad, 2023). Some well-studied water-soluble vitamins consist of vitamin C, and the vitamin B complex, which includes thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, and cobalamin (Lykstad, 2023). Vitamin C is vital to collagen formation, iron absorption, immune function, bone formation, and is found in "citrus fruits, berries, tomatoes, potatoes, and green leafy vegetables". Recommended daily intake is 40-120 mg per day. The vitamin B complex thiamine, riboflavin, niacin etc. all aid in functions in the body. Vitamin B1 plays a large role in glucose breakdown as a cofactor for multiple enzymes involved in the process such as branched chain ketoacid dehydrogenase (Lykstad, 2023). Vitamin B1(Thiamin) is vital to aerobic tissues in the brain, heart, and nerves. Constant deficiency of daily values can cause severe damage to the body, which we will discuss later. Vitamin B2, also called riboflavin, is important for redox reactions and is found in dairy products, fortified grains, and fruits and vegetables, with a daily recommended intake of 1.1 mg/day for men, .9-1.1 mg/d for women increasing during pregnancy to between 1.4-1.6 mg/d (Espinosa-Salas, 2023). Similarly, vitamin B3 niacin is crucial to redox reactions, and is found in fish, legumes, meat, nuts, & milk, with a recommended daily dose of 16mg/d for men and 14mg/d for women (Espinosa-Salas, 2023). Since the B complex vitamins are water soluble, the body cannot keep storage of them for long periods of time meaning that their continual

consumption through diet is vital to health (Espinosa-Salas, 2023). As mentioned earlier, thiamine plays an essential role in the body, as a water-soluble vitamin, deficiency can cause irreparable damage.

Nutrition and Development

Optimal neurocognitive development is the outcome of the parallel relationship of proper nutrition and environment interaction during the period of most rapid brain development: the first few years of life. During early development, prenatal and postnatal, five developmental processes rely on proper nutrition: neuron proliferation, axon and dendrite growth, synapse pruning and function, myelination, and apoptosis (Prado et al. 2014). Nutrition and environmental stimulation have interacting effects. Nutrition is dependent on environmental input to refine brain processes: environmental input activates cells, retains and strengthens synaptic connections, while cells and synapses that are unused are eliminated (Prado et al. 2014, Lykestad, 2023; Espinosa-Salas, 2023). Deficiencies in a nutrient are dependent on timing and the degree of nutrient deficiency, meaning that the adequate amount of a nutrient is met at a specific time in brain development (Cusick, 2016; Prado et al. 2014). Proof of a single nutrient's effects on brain development is hard to demonstrate due to multiple nutrient deficiency in at-risk populations, as well as confounding variables such as poverty and stress (Cusick 2016; Fattal-Valevski 2006). Yet observational examples have been shown in real world case studies.

In Israel a manufacturing error of a soy-based infant formula exemplified the detrimental impacts of acute vitamin B1 deficiency. In a retrospective cohort study, researchers age-matched 30 healthy children with no significant nutritional history to 39 children who had been fed faulty infant formula during the first two years of life (Harel et al., 2017). Among the children who survived the severe initial thiamine deficiency, all exhibited long-term neurodevelopmental

complications by age nine, including epilepsy, intellectual disabilities, and impairments in language and communication (Harel et al., 2017). Although this case lacks the necessary components of an experimental design to assess causation, researchers gained insight on an acute nutrient deficiency during a critical period, Vitamin B1 thiamine. Specifically, deficient thiamine can lead to impairment in neurological function and subsequently impair systematic linguistic development in infants due to its role in synaptic formation (Prado et al. 2014). Non-human species' neural regions (homologous to areas known to subserve language functioning in humans) are damaged by thiamine deficiency specifically in the prefrontal cortex and hippocampus (Baldwin et al. 2024; Langlais & Savage, 1995). If comparable to humans, thiamine deficiency threatens language development in infants (Baldwin et al. 2024).

The role of thiamine deficiency in development of language concerning, as thiamine deficiency is endemic in many global areas. Due to the prevalence of thiamine antagonists & reliance on parboiled rice, countries in Southeast Asia have become alarmed to the potential impacts of thiamine deficiency and the prevention of the condition. (Fattal-Valevski 2011; Whitfield et al. 2017; Baldwin et al. 2024).

Thiamine

Thiamine is a water-soluble B vitamin that occurs naturally in legumes, meat, nuts, milk, fortified bread and grains. Thiamine supplementation is a treatment for many health conditions such as beriberi, Wernicke's encephalopathy, and cardiovascular disease. However insufficient thiamine appears as a contributor to many neurological, gastrointestinal, and cardiovascular conditions. Due to increased risk of health conditions from thiamine deficiency it is important to maintain the recommended daily intake of thiamine, because the human body has limited storage and rapidly exerts thiamine. First the micronutrient enters the body existing in food, then is

absorbed in the jejunum and ileum (parts of the small intestine) through active diffusion in low concentrates, and passive diffusion in high concentrates (De Jong et al. 2004). It exists in the body in its active form called TPP (thiamine pyrophosphate). TPP is transported throughout the body within plasma and red blood cells in the circulatory system, where it is able to assist in actions. Thiamine is important in multiple body mechanizations: metabolism, the Krebs cycle, glycolysis, and the pentose phosphate pathway (Martel, 2024). First, thiamine works with enzymes to metabolize carbohydrates, lipids, and branch chained amino acids (Martel, 2024). TPP is a main cofactor that activates enzymes that play a role in producing amino acids and glucose derived neurotransmitters from carbohydrates metabolism (Harel et al. 2017).

Neurocognitively, thiamine pyrophosphate is essential for synapse formation, myelination of nerve cell membranes, axon growth, maintaining stability of nerve membranes during development and apoptosis (Harel et al. 2017). As thiamine aids in many functions, an imbalance between the amount of thiamine your body needs to function, and the amount it is receiving can cause serious impacts on the body. The recommended daily intake of thiamine is 1.2mg for men, 1.1mg for women, increasing to 1.4mg for pregnant & lactating women. For infants 0-6 months, .2 mg is the recommended daily intake of thiamine. If recommended daily intake values are not met continually, the body may develop a thiamine deficiency disorder (National Institute of Medicine, 1998).

Thiamine Deficiency Disorders (TDDs) are often misdiagnosed as other illnesses due to the relationship of symptoms with impoverished conditions such as repeated illness, and mortality. Due to the micronutrient's role's role in glucose breakdown, deficiency can contribute to adenosine triphosphate (ATP) depletion and often affects highly aerobic tissues such as the brain, nerves, and heart first." (Lykstad, 2023). Deficiency can lead to heart issues, wet beriberi

can cause loss of function (Fattal-Valevski, 2005; Wilder, 1943), deficiency can lead to the condition wet beriberi, characterized by high-output heart failure, edema, and dyspnea on exertion. Thiamine deficiency can be present in infants through the nervous system, Wernicke-Korsakoff syndrome appears as a disordered ability to acquire new information due to damage to the brains thalamus and hypothalamus from lacking vitamin B1 (National institute of Neurological disorders).

There are two main dietary causes of thiamine deficiency among infants. First, if a breastfeeding mother's diet lacks sufficient thiamine—recommended at 1.2 mg/day during lactation—the infant may not receive adequate amounts (Whitfield, 2021). Second, deficiency can result from a defective infant formula, which is the primary source of nutrition for non-breastfed infants. In 2003, a defective infant formula manufactured and distributed in Israel without the micronutrient vitamin B1, highlighted the consequences of thiamine deficiency on infant health.

In Israel, several infants were hospitalized with symptoms ranging from fever, vomiting, Nystagmus, respiratory symptoms, lethargy abnormal distention, subsequently two of the children died from cardiomyopathy (Fattal-Valevski, 2005). Through epidemiological review of the similar symptoms between the infants hospitalized, it was found that they had all been fed the same soy-based infant formula (Fattal-Valevski, 2005). The Israeli Ministry of Public Health was notified of the commonality between cases, and the product was tested for thiamine content of which it contained an undetectable level.

The infants who were hospitalized underwent an erythrocyte transketolase activity assay, wherein the extent of thiamine deficiency is expressed in percentage stimulation compared with baseline level (the thiamine pyrophosphate effect [TPPE]). Normal values range from 0% to

15%; a value of 15% to 25% indicates thiamine deficiency, and >25% indicates severe deficiency." (Fattal-Valevski, 2005). Thiamine deficiency was diagnosed through abnormal transketolase activity (TPPE > 15%). Infants were treated with 50mg dosage of intramuscular thiamine and advised to switch infant formulas (Fattal-Valevski, 2005).

The incident in Israel provided an opportunity to isolate the consequences of inadequate levels of thiamine on infants' development, bringing renewed attention to the importance of the recommended daily thiamine allowance during infancy (Harel et al, 2017). Nursing infants is 0.2 mg/day, 0.3mg/day for 7-12 months, and 0.5 mg/day for toddlers between 1-3 years. Importantly, thiamine requirements correspond with body size due to rapid growth and development during the critical developmental period of the first 4 years of life. If the thiamine allowance is not met, motor and language disorders were found to be significantly correlated in follow-up data collection of exposed children ages 5-7 (Harel et al, 2017; Prado & Dewey, 2014). Since the study in Israel lacked randomization, researchers were unable to conclude that the lack of thiamine played a causal role in the observed neurocognitive delays. Although this causal link might be less critical to establish in high-income countries where adequate diets are available and errors in formula manufacturing avoided, thiamine's role in neurocognitive development is especially relevant in regions like South and Southeast Asia, where thiamine deficiency disorders are widespread due to carbohydrate-based diets lacking whole grains, nuts, poultry, soybeans, peas, and fortified foods that carry the organic micronutrient thiamin (Espinosa-Salas 2023; Whitfield et al, 2021).

Thiamine Deficiencies in SE Asia

In Southeast Asia, 1 in every 2 children has at least one micronutrient deficiency (UNICEF, n.d). Thiamine deficiency remains a significant public health concern in Southeast

Asia, particularly among mothers and infants in Cambodia (Coats, 2012). Thiamine deficiency disorders are extremely prevalent in Southeast Asia, in a study done by Coers et al. thiamin deficiency was evident in whole blood Thiamine Diphosphate concentrations of Cambodian mother-infant pairs (Coers et al. 2012). This can lead to fatal cases of infant thiamin deficiency disorders such as beri beri, which is common in areas where dietary sources of thiamin are low (Whitfield, 2015). Beri beri, while rarely seen in developed countries, is endemic in Southeast Asia. A study specific to Cambodia notes that there are three suspected reasons why thiamine deficiency is prevalent in Cambodian mothers and infants. First, white polished rice is a dietary staple, whereas the vitamin B containing husk is removed. Secondly, rice is not parboiled, a process that contributes to less carbohydrates, more protein and fiber. Third of all, there is a lack of dietary diversity (Whitfield et al, 2015). While these issues in diet can go unnoticeable in the mother, while breastfeeding the mother's suboptimal thiamin intake causes low breast milk thiamin concentrations (Whitfield et al, 2015). Thiamine deficiencies among childbearing women are extremely rare in countries with mandatory thiamine grain fortification and a diverse diet that includes thiamine-rich animal products (Berner, 2014). Subsequently beri beri is extremely rare in developed countries, leading researchers to suspect research on thiamin intervention in developing countries is necessary to prevent infant mortality (Coers et al, 2012). The study in Israel showed that thiamine was necessary for infant survival, but it left researchers curious if supplementation of thiamine for babies who may be at risk of deficiency could protect and even aid brain development.

Recent Experiments

A team of researchers launched a randomized controlled trial in 2019 to investigate the developmental impact of thiamine supplementation on lactating mothers and their infants in rural

Cambodia (Whitfield et al., 2019). This double-blind, four-arm parallel study aimed to determine how maternal thiamine supplementation affects breast milk thiamine concentrations and, in turn, infant cognitive outcomes. The four treatment groups received either 0, 1.2, 2.4, or 10 mg of thiamine daily from 2 to 24 weeks postpartum. Participant demographic, socioeconomic, and health information were assessed at the beginning of the trial. The trial's primary objective was to establish the dose-response curve at which additional maternal thiamine intake no longer significantly increased thiamine concentrations in breastmilk at 24 weeks postpartum.

A secondary objective focused on comparing infant neurocognitive development—measured using the Mullen Scales of Early Learning (MSEL)—between the 0 mg and 10 mg thiamine groups. Follow-up assessments occurred at 12, 24, and 52 weeks. The MSEL evaluated infants across five domains: fine motor, gross motor, visual reception, and receptive and expressive language. In addition to raw scores, researchers used Early Learning Composite (ELC) scores and t-scores standardized against high-income country norms to assess development. Initial results from this study showed that higher maternal thiamine supplementation was significantly associated with better infant receptive and expressive language scores at 24 weeks, with the 10 mg dosage providing the greatest benefit. No significant treatment group differences were observed relative to the control condition on measures of fine motor, gross motor, or visual reception development. However, by 52 weeks—six months after supplementation ended—the significant language benefits realized at 6-months had faded, and infants' receptive and expressive language t-scores declined significantly relative to international norms. As shown in Figure 1, this pattern suggests that the early benefits of thiamine supplementation on language development may be time-limited and vulnerable to post-intervention environmental or nutritional factors.

Because scores in other developmental areas remained relatively stable following the cessation of thiamine supplementation at 6-months, it raised the following critical questions: Why did infants' standardized MSEL language scores decline post-supplementation relative to international norms? Were there demographic factors that might account for sample level declines, but also help to account for why some infants did not show the same drop-off in standard scores? Assessing protective and inhibiting factors is essential to understanding how environmental influences may affect long-term developmental outcomes following early nutritional interventions.

Overview of Current Study

The goal of the present study was to determine the extent to which child and demographic factors might explain individual differences in the changes in infants' MSEL scores between the start of the trial, the endline at 6-months, and 12-months postpartum. We included a total of eight demographic / predictor variables within our analysis: infant sex, infant stunting, household income, mother's milk thiamine at 2 weeks, mother's highest education, father's highest education, mother's age, infant birth weight, and maternal depression at 2 weeks. We also included treatment group, and infant's endline scores within their respective subscale as a predictor for changes in infant MSEL scores between 6- and 12-months while also controlling infants' thiamine group in the RCT supplementation trial. The rationale for each of these potential predictors is presented in the following sections.

Stunting.

We chose to include stunting as a demographic to assess in relation to the drop off in MSEL measurements between 2, 24, and 52 weeks because of the relationship between stunting

and overall health. Stunting is related to undernutrition and an infant's diet is responsible for growth and development, especially after the introduction of complementary foods and eventually ceasing breastfeeding. Research has been done on the correlation between wealth inequality on chronic under-nutrition for Cambodian infants, in a 2006 study executed by The Demographic and Research Division for the Journal of Health, Population and Nutrition, researchers Rathavuth Hong, and Vinod Mishra. Undernutrition is caused by synergistic effects of inadequate intake of food and leads to effects on physical and cognitive growth (Pelletier, 1994). Using the 2000 Cambodia Demographic and Health Survey, Hong & Mishra estimated the effect of household wealth on moderate and severe stunting for Cambodian infants 0-59 months. Results of multinomial logistic regressions showed that "children in the poorest 20% of households were twice as likely to suffer from stunting than children in the richest 20% of households" with a 95% confidence interval (Hong, 2006). This finding points to a strong association between wealth inequality and chronic childhood undernutrition, and as discussed earlier: stunting impedes a child's neurocognitive development. We would like to see if children who are reported to be stunted show different language MSEL scores in comparison to children that were not reported as stunted.

Infant sex.

It has been shown that there are highly significant sex differences in brain-behavior relationships (Fenske et al. 2024). Research specifically has shown that females tend to perform better than males in measures of executive functioning (Fenske et al. 2024). Specifically, to the MSEL, studies on cross cultural adaptations of the measure have reported females scoring higher than males in the language subscales (Milosavljevic et al, 2019).

Household Income.

As referenced above, household income is related to the overall health and wellbeing of an infant, the poorer households reported higher rates of stunting (physical growth). Studies have been done in order to research the impact of wealth on cognitive development "children from economically disadvantaged families exhibit lower levels of cognitive functioning, academic achievement, and social development than children from more advantaged families." (Petterson, 2001). Household income is a protective factor, for example: low birthweight infants born into families in high socioeconomic status were at low risk of poor developmental outcomes compared to those born into disadvantaged environments (Prado et al. 2014; Torche F Echevarria G. 2011). Wealth impacts accessibility to nutritious foods, higher education, proper sanitation, all of which have been linked to aiding in development. Yet, in cases of supplementation, children within disadvantaged homes have shown more of a developmental response to interventions (Prado et al. 2014). For example, in Guatemala, the effect of supplementary protein drink on infant development was greatest among children of families in low socioeconomic backgrounds (Prado et al. 2014; Pollitt E. 1993). Yet, it is possible that language MSEL scores could falter at 1 year due to higher household income due to a parent's time for a child, as wealth can be related to occupation and time which impacts environmental stimulation. This is why we would like to include household wealth when assessing demographic factors in relation to the MSEL drop off in the language domains.

Maternal Depression.

We chose to include the demographic variable of maternal depression because we believe it connects to a caretaker's time, emotional availability, and may relate to resource availability and life circumstances. Children from low-income households often face cognitive and language delays due to limited resources and stimulation. Additionally, maternal depression affects

parenting quality, resulting in less responsive caregiving, which hinders secure attachment and emotional regulation (Petterson et al. 2001). Depression impacts interpersonal communication through emotional expressiveness and responsiveness (Murray et al. 1996). Associated adversity is thought to play a dynamic role in infant development to mothers with depression, socioeconomic factors amplify stressors like depression (Murray et al. 1996). These factors combine to create long-term developmental risks for children, increasing the likelihood of cognitive and language delays (Petterson et al, 2001). Considering the MSEL drop off in the language domain, we hypothesize that maternal depression will be predictive of change in scores from 6 to 12 months.

Parent Education

Parental education is the highest level of education attained by the mother and the father. This is known to impact the parent's expectations, beliefs, and behaviors (Davis, 2020). Highest education attainment also impacts each parents' income, as higher education provides higher paying job opportunities. Education inequality can impact generations due to the importance of education attainment on income, thus influence on socioeconomic stratification (Davis, 2020). We hypothesize that parents with higher education attainment will predict developmental gains from one time point to the next.

Hypotheses

These demographic variables were used to predict changes in MSEL scores between (1) the start of the supplementation trial and the endline at 6-months postpartum when supplementation was ceased, and (2) between the endline and 12-months postpartum, which was both after supplementation was stopped and the commencement of complimentary feeding.

In general, our prediction was that problematic levels on each of our demographic predictors (i.e., low birth weight, greater stunting, less parental education, less household income, and greater maternal depression) would be associated with less neurocognitive development at both 6- and 12-months postpartum.

Methods

Ethical Attainment

Ethical approval was obtained from the National Ethics Committee for Health Research, Cambodia; Mount Saint Vincent University Research Ethics Board, Canada (2017-141); and the University of Oregon Institutional Review Board, USA. Women provided written informed consent for themselves and their infant.

Participants

Mothers: Women (N = 335) were recruited through antenatal care visits at eight health centers throughout Kampong Thom province and entered the study at 2 weeks postpartum. Participants were healthy mothers (18–45 years old) to healthy, singleton, newborns. Mothers were not currently participating in any nutrition programs beyond normal care and had not consumed any thiamine-containing supplements in the four preceding months.

Infants: all infants were healthy exclusively breastfed newborns. There was a total of 335 infants: 161 female infants (48.1%) and 174 male infants (51.9%).

Data Collection Procedures

Participant demographic, socioeconomic, and health information were collected by healthcare workers at delivery, and by field workers at baseline (2 weeks postnatal), midline (12 weeks postnatal), endline (24 weeks postnatal), and at 1 year (52 weeks postnatal). Using calibrated instruments and standard protocols, infant anthropometric measurements (weight, length, and head circumference) were collected. Length-for-age Z scores were computed using the WHO Anthro plug-in for SPSS. (Measelle et al. 2021)

The impact of maternal thiamine supplementation dosage on infants' cognitive, motor, and language development across the first year is investigated through a double-blind, four-parallel-arm, randomized controlled trial, of healthy mothers of exclusively breastfed newborn infants in Kampong Thom, Cambodia. “At 2 weeks postnatal, women (n = 335) were randomized to one of four treatment groups to consume one capsule/day with varying amounts of thiamine for 22 weeks: 0, 1.2, 2.4, and 10 mg. At 2, 12, 24, and 52 weeks of age, infants were assessed with the Mullen Scales of Early Learning (MSEL) and the Caregiver Reported Early Development Instrument (CREDI)” (Measelle, et al., 2021). Using multiple regression and mixed effects modeling suggested that by 6 months of age, the highest maternal thiamine dose (10 mg/day) held significant benefits for infants' language development. In comparison to U.S. norms at 6 months, the infants achieved approximately similar standardized scores on the MSES. However, infants showed a significant failure to keep pace relative to U.S norms in both language domains following the removal of interventions after the trial completion, pointing towards a disparity in nutrition that the protective thiamine during the first 6 months could not offset.

Measures

Survey Data:

A vital part of the research was the questionnaire survey data, which was collected from infants’ primary caregivers at 2, 12, 24, and 52 weeks. For the purposes of the present study, maternal and paternal highest level of education and household income were derived. Maternal depression was assessed with the 2-item Patient Health Questionnaire (PHQ-2; Menea et al., 2016).

Anthropometric

Infant weight, length, and head circumference were measured using standard protocol. Length-for-age Z scores were computed using the WHO Anthro plug-in for SPSS.

Mullen's Scale of Early Learning

An adapted version of the Mullen's Scale for Early Learning (MSEL) was used to assess cognitive development for infants (Mullen, 1995). The MSEL was adapted by substituting potentially unfamiliar images, objects, and questions with examples that Cambodian infants or caregivers would recognize, to assess child outcomes in five developmental domains: gross motor, fine motor, visual reception, receptive language, and expressive language.

Each subscale consists of a set of performance-based items (typically 0 for failed and 1 for passed), presented in an order from less to more difficulty, where children are rated on whether they successfully complete task items to establish basal (three consecutive passed items) and ceiling (discontinuity after three consecutive unpassed items) ranges with which to render total raw scores. By summing a child's raw points on each MSEL scale, a raw score is created. Age-normed T-scores (M = 50, SD = 10) were created by converting raw scores on each subscale based on an original U.S. norming sample. The T-scores of the fine motor, expressive language, receptive language, and visual reception scales can also be combined to produce the Early Learning Composite (ELC) score (M = 200, SD = 30) (Measelle et al. 2021). These standardized tests of infant neurological and cognitive development were collected by field staff at all four time points.

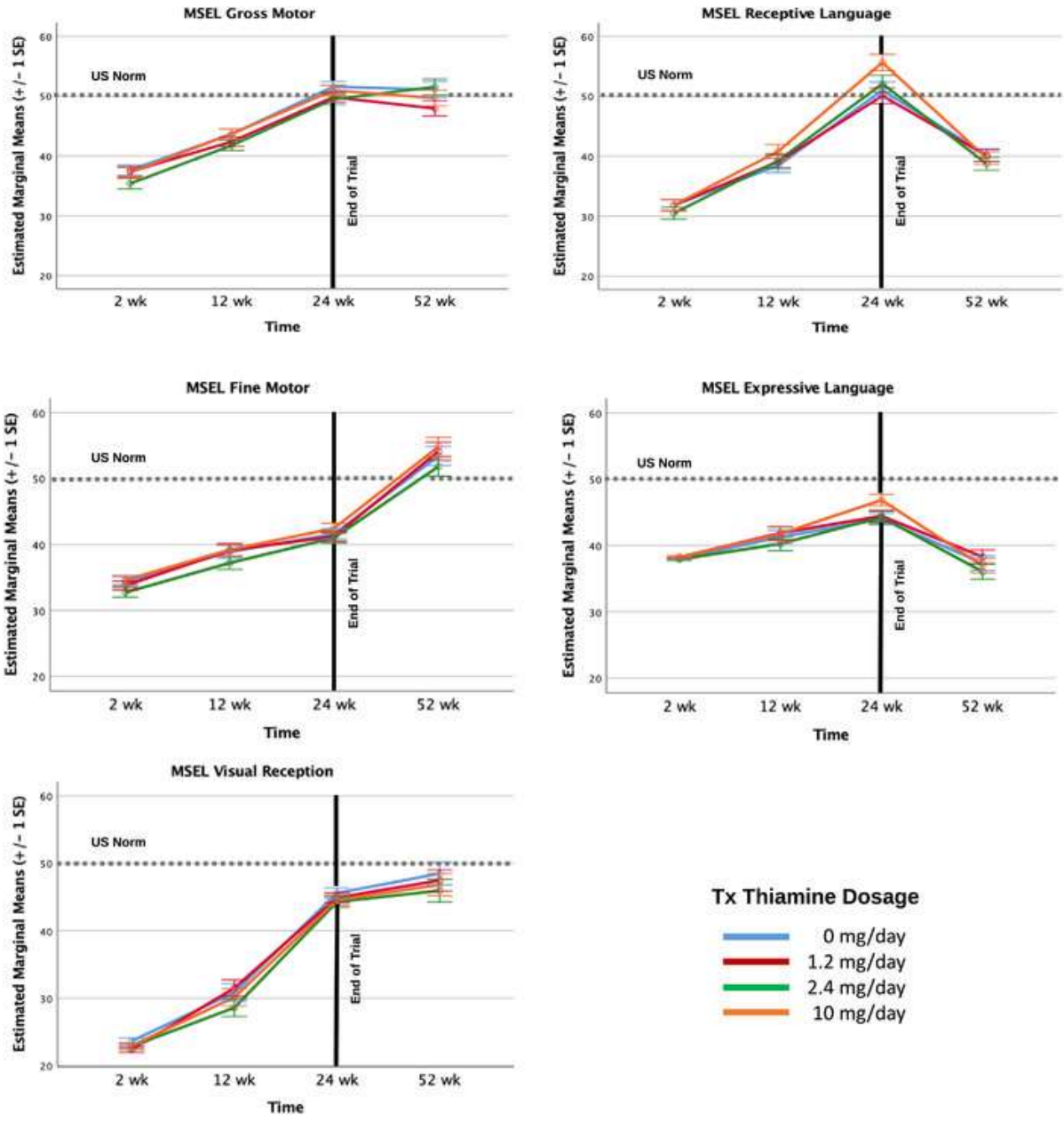
Data Analyses

Standard statistical methods were used to analyze the data for this thesis. Specifically, descriptive, correlational, and multiple regression analyses (performed in SPSS) are used to explore possible associations between demographic predictors and infants' standardized scores on the MSEL. At present, the key demographic variables to be tested include household income, caregiver health, and environmental exposures. We included a total of eight demographic / predictor variables within our analysis: infant sex, household income, mother's milk thiamine at 2 weeks, mother's highest education, father's highest education, mother's age, infant birth weight, and maternal depression at 2 weeks. In our primary analyses, regression models also included auto-regressive terms in order to measure change or cognitive development. Specifically, when predicting individual MSEL scores at endline, the model also included infants' score on the same MSLE scale at 2-week. When predicting MSEL scores at 12-months, infants' individual MSEL scores at 6-months were included in the model as controls.

Results

The primary aim of the present study was to determine if specific infant characteristics and familial demographic characteristics might help to explain the critical changes in MSEL scores between the end of the thiamine supplementation trial at 6-months post-partum and a follow-up assessment when infants were 12 months of age. As shown in Figure 1, infants showed sample level increases in the fine motor and visual reception domains and essentially stayed the same in the gross motor domain between 6- and 12-months. On average, however, infants showed a clear decline in both language domains between 6- and 12-months postpartum. Figure 1 also makes clear that there was considerable variability in infants' neurocognitive development between 6- and 12-months, which served as the primary rational for wanting to see which infant characteristics and familial demographic characteristics might account for these patterns.

Figure 1: Developmental trajectories of MSEL change by thiamine dosage levels.



Sample and Descriptive Statistics

Sample and descriptive statistics for the sample are presented in Table 1. The total sample size was N=335, including 161 female infants (48.1%) and 174 male infants (51.9%). The average weight in kilograms at birth was 3.11 kg (SD = 0.38). On average, infants' standardized height at 2-weeks postpartum, which was computed using international growth norms, suggested that infants were just smaller, Z-score mean = -.86, than the international mean

of Z= 0.0. However, there was significant variability, with 22.8% of the infants classifiable as clinically stunted.

On average, mothers averaged 28.12 (SD = 6.19) years of age at the time of enrollment and had an average of 1.46 (SD = 0.94) years of formal education, which was equivalent to a primary elementary to lower secondary school level of education. Fathers' education was, typically, similar to mothers. Household income was low relative to U.S. norms, with a mean annual income of $2,562.93 USD (SD = $2,584.20). It is worth noting, however, that the range of household income was noteworthy, which some households having 8 to 10 times the mean annual level.

Table 1 presents all five of the Mullen Scales at 2-, 12-, and 52-weeks postnatal. To summarize, the composite score is reviewed here. At baseline (2 weeks), infants had an average standardized (relative to North American norms) MSEL composite score of 126.61 (SD = 10.88), which increased to 183.51 (SD = 23.91) at 24 weeks and then slightly declined to 178.67 (SD = 35.02) at 12 months.

TABLE 1. Sample Characteristics and Descriptive Statistics

VARIABLES	**N or *M***	**(%) or (SD)**	**Min**	**Max**
Infant				
Sex (female)	161	48.1	-	-
Birth weight	3.11	(.38)	2.50	4.50
Stunting (Z-score)	-.86	(.92)	-3.63	1.68
Mother				
Age	28.12	(6.19)	18	44
Years Education	1.46	(.94)	0	4
2-week milk thiamine	129.12	(74.42)	12.64	482.13
Depression	.32	(.34)	0	2
Father				
Years Education	1.51	(.98)	0	4
Household				
Annual Income (USD)	2562.93	(2584.20)	200	19000
Infant MSEL Scores (Standardized)				

Baseline (2-Weeks)				
Gross Motor	36.93	(7.29)	26	55
Visual Reception	22.98	(3.68)	22	58
Fine Motor	34.09	(5.95)	27	57
Receptive Language	31.41	(8.08)	23	52
Expressive Language	38.14	(1.44)	30	47
MSEL Composite	126.61	(10.88)	102	162
Endline (24-Weeks)				
Gross Motor	50.4128	(7.27)	26	63
Visual Reception	44.9966	(6.53)	20	70
Fine Motor	41.7181	(6.46)	26	58
Receptive Language	52.0671	(11.48)	20	79
Expressive Language	44.7248	(6.81)	22	60
MSEL Composite	183.51	(23.91)	117	248
12-Months (52-Weeks)				
Gross Motor	50.17	(11.02)	20	66
Visual Reception	47.63	(13.73)	20	80
Fine Motor	53.79	(12.03)	20	80
Receptive Language	39.84	(8.55)	20	64
Expressive Language	37.41	(9.24)	20	66
MSEL Composite	178.67	(35.02)	87	260

Correlational Analyses

Intercorrelations among this study's selected predictors and between these predictors and MSEL scores are shown in Tables 2a and 2b, respectively. Infant stunting was positively correlated with infant birth weight ($r = .353$, $p < .01$), indicated that babies measuring longer at birth were also heavier. Infant stunting was also positively correlated with maternal education ($r = .127$, $p < .05$), but negatively with maternal depression ($r = –.104$, $p < .05$). Maternal depression was negatively correlated with father's highest education level ($r = -.123$, $p < .05$), indicating that maternal depression is associated with lower paternal education level. Mothers' highest education was positively correlated with fathers' highest education ($r = .441$, $p < .001$). Mother's highest education was positively correlated with household income ($r = .286$, $p < .05$), fathers' education being positively correlated with household income as well ($r = .309$, $p < .01$).

Additionally, mother's age is negatively correlated with mother's highest education level (r = -.375, p < .01), higher education is associated with lower age and reversely lower education is associated with older age.

Table 2a. Intercorrelations Among Predictors

	1	2	3	4	5	6	7	8	9
1. Infant Sex	-	-.038	.169**	.093	.008	.003	.049	-.035	-.046
2. Infant birth weight (kg)	-.038	-	.353**	.034	-.015	.016	.066	-.086	.016
3. Infant stunting (Z-score)	.169**	.353**	-	.067	.102	.058	-.071	.127*	-.104
4. Household income (USD)	.093	.034	.067	-	.309**	.060	-.024	.286**	-.056
5. Father's highest education level	.008	-.015	.102	.309**	-	.086	-.283**	.441**	-.123*
6. Mother's 2-week milk thiamine	.003	.016	.058	.060	.086	-	-.065	.072	-.009
7. Mother's age (Yrs.)	.049	.066	-.071	-.024	-.283**	-.065	-	-.375**	.187**
8. Mother's highest education level	-.035	-.086	.127*	.286**	.441**	.072	-.375**	-	-.099
9. Maternal depression at 2-weeks	-.046	.016	-.104	-.056	-.123*	-.009	.187**	-.099	-

Note.
** p<.05; **p<.01; **p<.001*

Correlations between predictor variables and infant MSEL scores appear in Table 2b. Notably, higher maternal milk thiamine levels at 2 weeks were positively associated with endline fine motor (r = .142, p < .05), receptive language (r = .176, p < .01), and expressive language scores (r = .127, p < .05). Infant birth weight was positively associated with endline composite (r = .152, p < .05). Maternal depression at 2 weeks was associated with endline visual reception (r = .157, p < .01), and endline composite scores (r = .128, p < .05). Infant sex was positively associated with 52-week expressive language scores (r = .128, p < .05), boys are coded as 1; girls coded as 2. Infant stunting was positively associated with 52 weeks gross motor scores (r = .151, p < .05), indicating that infants of greater length had higher gross motor scores at 12-months. Mother's age has a positive association with 52 weeks visual reception (r = .118, p < .05).

Notably, higher milk thiamine levels at two weeks are no longer significantly correlated with any MSEL subscale score nor the composite score at 52 weeks.

Table 2b. Intercorrelations Between Predictors and Infant MSEL Scores as 2- 24- and 52-weeks

	Endline Standardized MSEL Scale Scores						12-Mo Standardized MSEL Scale Scores					
	GM	VP	FM	RL	EL	COMP	GM	VP	FM	RL	EL	COMP
Infant Sex	.000	.074	-.017	.075	-.016	0.47	.033	.007	.029	.067	.128*	.063
Infant birth weight (kg)	.108	.103	.122*	.132*	.098	.152**	-.023	.045	.032	.030	.064	.053
Infant stunting (Z-score)	.020	.081	.094	.078	.047	.098	.151*	-.019	.027	.021	-.025	.000
Household income (USD)	-.072	-.090	-.053	-.009	.018	-.038	-.049	.033	.082	.041	.042	.062
Father's highest ED level	-.047	.011	.073	-.030	.071	.029	.003	.024	.072	.034	.045	.054
Mother's 2-week milk thiamine	-.077	-.003	.142*	.176**	.127*	.158**	-.034	.002	-.072	.030	.025	-.010
Mother's age (Yrs.)	.014	.130*	.020	-.021	.055	.047	-.016	.118*	.068	.054	.048	.095
Mother's highest ED level	-.079	-.048	.042	.021	.054	.024	-.026	-.059	-.017	-.018	-.021	-.039
Maternal depression at 2-weeks	.086	.157**	.051	.083	.109	.128*	-.030	.069	-.001	.087	.047	.061

Note.
** p<.05; **p<.01; **p<.001*

Change in MSEL Scores

A central motivation for the present study was to understand changes in infants' MSEL scores between 6- and 12-months, which corresponded with the end of our thiamine supplementation as study endline (6-months postnatal) and one year postnatal. Although the raw scores presented above suggest that infants showed cognitive gains in most domains, changes in the standardized scores relative to U.S. norms present a different picture. As shown in Table 3, from 6 to 12 months, infants showed mean increases in their standardized fine motor (M = 12.02, SD = 12.68) and visual reception scores (M = 2.36, SD = 14.27), while decreases were observed in the gross motor (M = -.45, SD 11.75), receptive language (M = –12.27, SD = 13.21) and expressive language domains (M = –7.49, SD = 10.92). Proportionally, a majority of infants improved in the fine motor (52.8%), gross motor (83.6%), and visual reception domains (62.9%).

The majority of infants decreased in the receptive (79.0%) and expressive language domains (70.6%). In terms of the MSEL composite score, infants decreased on average between 6- and 12-months (M=-5.38), with a larger proportion of infants decreasing (53.5%) in their overall MSEL performance relative to US norms.

Table 3. Sample Changes in Standardized MSEL Scores Between 6- and 12-months and the Proportion of Infants Shown a Decrease vs. Increase

MSEL Domain	*M*	(SD)	Range	% Decrease	% Increase
Gross Motor	-.45	(11.75)	-27 to 33	47.2	52.8
Visual Reception	2.36	(14.27)	-51 to 42	37.1	62.9
Fine Motor	12.02	(12.68)	-30 to 40	16.4	83.6
Receptive Language	-12.27	(13.21)	-48 to 22	79.0	21.0
Expressive Language	-7.49	(10.92)	-40 to 29	70.6	29.4
MSEL Composite	-5.38	(37.75)	-99 to 84	53.5	46.5

Note. Negative means indicated that the sample on average showed a decrease in their standardized score between endline and one year.

Regression Models for Endline Outcomes

This study's central analyses are presented in Tables 4 and 5. Specifically, "auto-regressive" multiple regression models were used to predict each of the MSEL scale scores at 6-monts/endline and at 12-months while controlling for infants' performance on a specific MSEL scale from a prior time-point. This autoregressive term essentially meant that all other variables in the model were predicting change on MSEL performance between the two time points modeled. Table 4 presents the result of models used to predict each of the MSEL scores at study endline while controlling for MSEL scores when infants were 2-weeks of age (our pre-intervention baseline). With the exception of the models predicting visual reception and expressive language, the autoregressive term at 2-weeks in the other models was a significant predictor of the same MSEL score at endline. With only a few exceptions, the child and demographic predictors failed to predict significant change in the various MSEL models.

Exceptions included maternal milk thiamine, which was a significant positive predictor of endline receptive language (β = .168, p = .003), fine motor (β = .129, p = .026), and expressive language (β = .127, p = .031) scores. Specifically, great concentrations of milk thiamine at 2-week postpartum, just before the supplementation trial started, were associated with higher scores in these domains. Contrary to prediction, maternal depression was associated with significant gains in endline visual reception by 6 months (β = .155, p = .009).

Table 4. Regression Models Predicting Endline MSEL Scores While Controlling for 2-week MSEL Scores

	B	**SE B**	**b**	**t**	**p-value**	**95% CI LB**	**95% CI UB**
Model/Predictors							
Endline Gross Motor							
2-week MSEL – Gross Motor	.181	.058	.181	3.135	.002	.068	.295
Thiamine Tx Group	.022	.107	.012	.203	.839	-.190	.233
Infant Sex	.014	.858	.001	.016	.987	-1.674	1.703
Infant birth weight (kg)	2.078	1.217	.107	1.708	.089	-.316	4.473
Infant stunting (Z-score)	-.002	.503	.000	-.004	.997	-.993	.989
Household income (USD)	.000	.000	-.065	-1.067	.287	-.001	.000
Father's highest ED level	.146	.505	.019	.289	.772	-.847	1.139
Mother's 2-week milk thiamine	-.008	.006	-.080	-1.368	.172	-.020	.004
Mother's age (Yrs.)	-.042	.076	-.036	-.557	.578	-.191	.107
Mother's highest ED level	-.372	.532	-.048	-.699	.485	-1.420	.676
Maternal depression at 2-weeks	1.802	1.361	.079	1.325	.186	-.876	4.480
	R^2=.06, $F(11, 286) = 1.82$, $p = .050$						
Endline Visual Reception							
2-week MSEL – Vis Recep	.058	.103	.032	.563	.574	-.145	.261
Thiamine Tx Group	-.086	.096	-.051	-.892	.373	-.275	.104
Infant Sex	1.063	.767	.081	1.386	.167	-.447	2.572
Infant birth weight (kg)	1.462	1.090	.083	1.341	.181	-.683	3.606
Infant stunting (Z-score)	.403	.452	.057	.892	.373	-.486	1.293
Household income (USD)	.000	.000	-.118	-1.951	.052	-.001	.000
Father's highest ED level	.552	.451	.080	1.226	.221	-.335	1.439

Mother's 2-week milk thiamine	-.001	.005	-.008	-.142	.887	-.011	.010
Mother's age (Yrs.)	.128	.068	.122	1.893	.059	-.005	.262
Mother's highest ED level	.112	.476	.016	.236	.814	-.825	1.049
Maternal depression at 2-weeks	3.189	1.217	.155	2.620	.009	.793	5.584
	R^2=.07, F(11, 286) = 2.06, p = .023						
Endline Fine Motor							
2-week MSEL – Fine Motor	.137	.062	.127	2.192	.029	.014	.259
Thiamine Tx Group	.123	.095	.074	1.290	.198	-.065	.310
Infant Sex	-.250	.757	-.019	-.330	.741	-1.740	1.240
Infant birth weight (kg)	1.678	1.076	.097	1.560	.120	-.440	3.796
Infant stunting (Z-score)	.429	.445	.061	.964	.336	-.447	1.306
Household income (USD)	.000	.000	-.093	-1.531	.127	-.001	.000
Father's highest ED level	.547	.445	.080	1.228	.220	-.329	1.423
Mother's 2-week milk thiamine	.012	.005	.129	2.234	.026	.001	.022
Mother's age (Yrs.)	.079	.067	.076	1.182	.238	-.053	.212
Mother's highest ED level	.384	.471	.056	.815	.416	-.543	1.312
Maternal depression at 2-weeks	.832	1.201	.041	.692	.489	-1.533	3.196
	R^2=.08, F(11, 286) = 2.13, p = .019						

Table continues…

	B	**SE B**	**b**	**t**	**p-value**	**95% CI LB**	**95% CI UB**
Model/Predictors							
Endline Receptive Language							
2-week MSEL – Rec Lang	.199	.081	.141	2.473	.014	.041	.358
Thiamine Tx Group	.401	.166	.136	2.410	.017	.073	.728
Infant Sex	2.039	1.324	.089	1.541	.124	-.566	4.644
Infant birth weight (kg)	3.217	1.887	.104	1.705	.089	-.498	6.932
Infant stunting (Z-score)	.318	.779	.025	.408	.683	-1.215	1.851
Household income (USD)	.000	.000	-.032	-.536	.592	-.001	.000
Father's highest ED level	-.816	.780	-.067	-1.046	.296	-2.350	.719
Mother's 2-week milk thiamine	.027	.009	.168	2.947	.003	.009	.046
Mother's age (Yrs.)	-.043	.117	-.023	-.365	.715	-.274	.188
Mother's highest ED level	.541	.823	.044	.658	.511	-1.079	2.162
Maternal depression at 2-weeks	2.421	2.112	.067	1.146	.253	-1.736	6.578

	R^2=.10, F(11, 286) = 2.98, p < .001						
Endline Expressive Language							
2-week MSEL – Exp Lang	-.402	.276	-.084	-1.454	.147	-.945	.142
Thiamine Tx Group	.175	.101	.100	1.734	.084	-.024	.374
Infant Sex	-.174	.803	-.013	-.217	.829	-1.755	1.407
Infant birth weight (kg)	1.698	1.141	.093	1.488	.138	-.548	3.945
Infant stunting (Z-score)	.069	.473	.009	.145	.884	-.862	.999
Household income (USD)	-.000	.000	-.029	-.472	.638	.000	.000
Father's highest ED level	.530	.472	.074	1.122	.263	-.399	1.459
Mother's 2-week milk thiamine	.012	.006	.127	2.165	.031	.001	.023
Mother's age (Yrs.)	.096	.071	.088	1.356	.176	-.043	.236
Mother's highest ED level	.461	.499	.064	.924	.356	-.521	1.443
Maternal depression at 2-weeks	1.768	1.283	.082	1.379	.169	-.756	4.293
	R^2=.06, F(11, 286) = 1.78, p = .057						
Endline MSEL Composite							
2-week MSEL – Composite	.234	.125	.108	1.877	.062	-.011	.480
Thiamine Tx Group	.591	.348	.096	1.699	.090	-.094	1.276
Infant Sex	2.772	2.767	.058	1.002	.317	-2.675	8.220
Infant birth weight (kg)	7.720	3.955	.120	1.952	.052	-.065	15.506
Infant stunting (Z-score)	1.255	1.628	.048	.771	.442	-1.950	4.460
Household income (USD)	-.001	.001	-.078	-1.306	.193	-.002	.000
Father's highest ED level	.759	1.631	.030	.465	.642	-2.451	3.970
Mother's 2-week milk thiamine	.049	.020	.144	2.520	.012	.011	.088
Mother's age (Yrs.)	.279	.247	.072	1.131	.259	-.206	.764
Mother's highest ED level	1.591	1.724	.062	.923	.357	-1.802	4.985
Maternal depression at 2-weeks	8.512	4.401	.113	1.934	.054	-.150	17.174
	R^2=.10, F(11, 286) = 2.77, p = .002						

Regression Models for 12-Month Outcomes

Regression models predicting 12-month MSEL scores controlling for endline performance at 6-months are summarized in Table 5. With the exception of infant expressive

language, where the autoregressive effect was borderline significant, all other MSEL scores at 6-months were significantly predictive of higher MSEL scores at 12 months. Among the other predictors in the models, infant sex significantly predicted significant gains in expressive language at 12 months (β = .175, p = .004), with females showing higher scores. No other predictors consistently emerged across domains. Higher infant birthweight was significantly predictive of more gross motor development between 6- and 12-months whereas less stunting at birth was associated with greater gains in gross motor development between 6- and 12-months. Beyond these few significant predictors, none of the other demographic variables predicted significant change in MSEL scores between 6- and 12-months.

Table 5. Regression Models Predicting 12-Month MSEL Scores While Controlling for Endline MSEL Scores

	B	**SE B**	**b**	**t**	**p-value**	**95% CI LB**	**95% CI UB**
Model/Predictors							
12-Month Gross Motor							
Endline MSEL – Gross Motor	.351	.091	.228	3.878	<.001	.173	.530
Thiamine Tx Group	-.020	.166	-.007	-.118	.906	-.346	.307
Infant Sex	-.126	1.308	-.006	-.096	.923	-2.702	2.450
Infant birth weight (kg)	-3.691	1.865	-.126	-1.979	.049	-7.364	-.019
Infant stunting (Z-score)	2.359	.768	.197	3.070	.002	.847	3.872
Household income (USD)	.000	.000	-.043	-.706	.481	-.001	.000
Father's highest ED level	.299	.765	.026	.391	.696	-1.208	1.806
Mother's 2-week milk thiamine	-.005	.009	-.031	-.529	.597	-.024	.014
Mother's age (Yrs.)	-.055	.115	-.031	-.475	.635	-.281	.172
Mother's highest ED level	-.661	.814	-.056	-.812	.418	-2.264	.942
Maternal depression at 2-weeks	-.595	2.063	-.017	-.289	.773	-4.657	3.466
	R^2=.09, F(11, 274) = 2.52, p = .005						
12-Month Visual Reception							
Endline MSEL – Vis Recep	.295	.130	.139	2.263	.024	.038	.552
Thiamine Tx Group	-.099	.212	-.028	-.468	.640	-.517	.318
Infant Sex	.860	1.674	.031	.514	.608	-2.435	4.155

Infant birth weight (kg)	.501	2.377	.014	.211	.833	-4.179	5.181
Infant stunting (Z-score)	-.461	.982	-.031	-.470	.639	-2.395	1.473
Household income (USD)	.000	.000	.053	.831	.407	.000	.001
Father's highest ED level	.730	.981	.051	.744	.457	-1.202	2.663
Mother's 2-week milk thiamine	-.001	.012	-.004	-.060	.952	-.024	.023
Mother's age (Yrs.)	.194	.148	.087	1.308	.192	-.098	.485
Mother's highest ED level	-.976	1.037	-.067	-.941	.347	-3.018	1.066
Maternal depression at 2-weeks	1.654	2.663	.038	.621	.535	-3.588	6.896
	R^2=.05, F(11, 274) = 1.26, p = .251						
12-Month Fine Motor							
Endline MSEL – Fine Motor	.351	.114	.186	3.089	.002	.127	.575
Thiamine Tx Group	.101	.185	.032	.548	.584	-.263	.466
Infant Sex	.674	1.457	.028	.463	.644	-2.195	3.543
Infant birth weight (kg)	.804	2.076	.025	.387	.699	-3.284	4.891
Infant stunting (Z-score)	.006	.856	.000	.007	.994	-1.680	1.692
Household income (USD)	.000	.000	.086	1.375	.170	.000	.001
Father's highest ED level	.973	.856	.077	1.137	.257	-.712	2.658
Mother's 2-week milk thiamine	-.020	.011	-.113	-1.879	.061	-.041	.001
Mother's age (Yrs.)	.119	.128	.061	.930	.353	-.133	.372
Mother's highest ED level	-.732	.905	-.057	-.810	.419	-2.514	1.049
Maternal depression at 2-weeks	-.445	2.290	-.012	-.194	.846	-4.954	4.064
	R^2=.06, F(11, 286) = 1.71, p = .071						

Table continues.

	B	**SE B**	**b**	**t**	**p-value**	**95% CI LB**	**95% CI UB**
Model/Predictors							
12-Month Receptive Language							
Endline MSEL – Rec Lang	.121	.047	.160	2.592	.010	.029	.214
Thiamine Tx Group	-.113	.135	-.050	-.832	.406	-.379	.154
Infant Sex	.980	1.062	.056	.923	.357	-1.110	3.070
Infant birth weight (kg)	.236	1.511	.010	.156	.876	-2.738	3.209
Infant stunting (Z-score)	.045	.621	.005	.073	.942	-1.178	1.269
Household income (USD)	.008	.000	.026	.410	.682	.000	.001
Father's highest ED level	.237	.620	.026	.382	.703	-.983	1.457
Mother's 2-week milk thiamine	.001	.008	.008	.134	.894	-.014	.016
Mother's age (Yrs.)	.053	.093	.038	.567	.571	-.130	.236
Mother's highest ED level	-.328	.657	-.035	-.499	.618	-1.621	.966

Maternal depression at 2-weeks	1.970	1.666	.072	1.182	.238	-1.310	5.251
	R^2=.04, F(11, 286) = 1.11, p < .357						
12-Month Expressive Language							
Endline MSEL – Exp Lang	.148	.082	.109	1.799	.073	-.014	.310
Thiamine Tx Group	-.101	.143	-.042	-.703	.482	-.383	.181
Infant Sex	3.256	1.124	.175	2.896	.004	1.043	5.470
Infant birth weight (kg)	1.842	1.600	.074	1.151	.251	-1.308	4.991
Infant stunting (Z-score)	-.827	.660	-.082	-1.253	.211	-2.127	.473
Household income (USD)	.003	.000	.009	.150	.881	.000	.000
Father's highest ED level	.367	.660	.038	.557	.578	-.931	1.666
Mother's 2-week milk thiamine	.003	.008	.020	.328	.743	-.013	.019
Mother's age (Yrs.)	.026	.099	.017	.262	.794	-.169	.221
Mother's highest ED level	-.395	.699	-.040	-.566	.572	-1.771	.980
Maternal depression at 2-weeks	.944	1.773	.032	.532	.595	-2.546	4.433
	R^2=.05, F(11, 286) = 1.43, p = .157						
12-Month MSEL Composite							
Endline MSEL – Composite	.362	.090	.242	4.018	<.001	.184	.539
Thiamine Tx Group	-.343	.538	-.037	-.637	.524	-1.402	.716
Infant Sex	5.311	4.228	.075	1.256	.210	-3.012	13.635
Infant birth weight (kg)	1.906	6.044	.020	.315	.753	-9.992	13.804
Infant stunting (Z-score)	-1.309	2.482	-.034	-.527	.598	-6.195	3.577
Household income (USD)	.001	.001	.064	1.030	.304	-.001	.003
Father's highest ED level	2.276	2.474	.061	.920	.358	-2.594	7.146
Mother's 2-week milk thiamine	-.026	.031	-.051	-.848	.397	-.086	.034
Mother's age (Yrs.)	.371	.372	.065	.999	.319	-.360	1.103
Mother's highest ED level	-2.598	2.623	-.069	-.990	.323	-7.762	2.566
Maternal depression at 2-weeks	2.891	6.679	.026	.433	.665	-10.258	16.039
	R^2=.09, F(11, 286) = 2.32, p = .010						

Discussion

As part of the larger research study designed to investigate the potential benefits of maternal thiamine supplementation on various child outcomes across the first year of life (Whitfield et al., 2019), infants were assessed with the Mullen's Scale of Early Learning (MSEL) at 12 months—six months after the supplementation trial ended—to evaluate changes in their cognitive scores following the intervention (Measelle et al., 2021). The outcome of the testing at 52 weeks showed that the majority of infant's standardized MSEL scores increased in the gross motor, fine motor, and visual reception domains, yet a majority of infants declined significantly in the expressive language and receptive language domains, as well as on the MSEL early learning composite score. These findings from the original study prompted the central questions undertaken in the present investigation, namely, could child or demographic factors be identified that might explain this fall off in some but not all of the MSEL neurocognitive development domains. Specifically, the main aim of this study was to determine whether a panel of child and demographic data might predict change in any subscale of the MSEL between (1) the start of the trial at 2-weeks and the study endline at 6-months postpartum, and (2) more centrally, between the trial endline and the follow-up assessment at 12 months. A total of eight predictor variables were tested in the study's central analysis: infant sex, household income, mother's milk thiamine at 2 weeks, mother's highest education, father's highest education, mother's age, infant birth weight, and maternal depression at 2 weeks.

As highlighted both in the original study (Measelle et al., 2021) and explored further in the current study, there were both increases and decreases in infants' standardized scores between 6- and 12-months, including considerable individual variability. In the gross motor, fine motor, and visual perception subscales, a larger proportion of infants increased in score between

6 and 12 months. In expressive language, receptive language, and composite scores, the majority of infants experienced a decline from endline to 12 months.

In the parent study, the fact that the language domains saw the largest change in scores following cessation of intervention was suggestive of the likely importance of adequate thiamine on developing language systems (Measelle et al. 2021). The timing of nutrient adequacy is vital for critical periods in development (Cusick, 2016; Prado et al. 2014). Thiamine is important for synaptic formation and strengthening connection between cells, without thiamine the developing brain lacks the metabolic aid in synaptic formation (Prado et al. 2014). The recommended daily intake (AI) of thiamine for lactating mothers is 1.4 mg/day, and for infants 0-6 months is .2mg/daily (IM, 1998). Until 6 months, infants rely on their mother's diet for .2 mg a day, however at 7 months infants AI increases to .3mg/daily (IM, 1998). After 6 months, not only does the infants recommended adequate intake rise .1 mg, but infants also begin to switch to complementary feeding. At 6 months in the clinical trial, mothers were no longer receiving thiamine supplements, so the infants were experiencing three changes: end of the clinical thiamine supplementation, rise in recommended adequate intake, and switch to regular foods. Due to the prevalence of thiamine antagonists (thiaminase-rich fish and betel nut), reliance on parboiled rice and lack of dietary diversity, the switch to complementary feeding may have undercut the required amount of thiamine needed to support aspects of development that are metabolically demanding, in particular, neurocognitive development (Whitfield et al., 2018; Muthayya et al. 2014). Without continued supplementation, it is plausible that neurocognitive gains could not be metabolically sustained during the critical period of language development after 6 months, which would help to explain the fall-off in language subscales (Fattal-Valevski 2011; Whitfield et al. 2017; Measelle et al 2021; Baldwin et al. 2024).

To better understand how changes in thiamine intake affected development over time, in the primary analysis of the current study, we examined a panel of demographic factors to see if they might account for changes in cognitive development between 2 and 24 week, the period of our trial, and between the endline at 24 weeks and a final assessment at 52 weeks. Contrary to prediction, there were no clear or consistent demographic variables that predicted change in infant MSEL scores from one time point to the next (2 to 24 weeks, and 24 to 52 weeks). Although demographic factors such as household income or parental education have been found in other studies to predict infant cognitive development (Schanzenbach, 2020), it is possible that other factors entirely may have been more important at this stage of development.

Although we did not have consistent predictors of change beyond what we might have expected due to chance, there were several instances where the modeled predictors helped explain changes in infant neurocognitive scores in specific MSEL domains. For example, our regression results revealed that mother's milk thiamine at 2 weeks was significantly predictive of change in several MSEL domains between 2-weeks and the endline at 6-months. At 2 weeks, mother's milk thiamine levels were assessed to measure thiamine levels via breast milk before supplementation as well as to provide an estimate of infants' access to thiamine during the pre- and early postnatal periods (Whitfield et al., 2019; Baldwin et al. 2024). Consistent with prediction, our results suggest that higher maternal milk thiamine levels at 2 weeks significantly predicted greater growth on both language subscales as well as in the fine motor domain between 2- and 24-weeks relative to infants whose mothers had lower milk thiamine concentrations at 2-weeks. Prior research suggests that mothers who consume thiamine-poor diets would likely have lower levels of thiamine in their breast milk (Whitfield, 2017). Importantly, given infants' reliance on maternal breastmilk as their sole source of nutrition during the first 6 months of life,

low levels of thiamine at the start of the trial may have predisposed some infants to slower or more limited neurocognitive development. This pattern did not hold, however, when predicting change in infants' MSEL scores between the study's endline at 6-months and the 12-month assessment. Specifically, maternal milk thiamine at 2-weeks was not predictive of change in any MSEL domain suggesting that any potential advantage conferred prenatally and detectible at 6-months was largely gone or undetectable by one year postpartum. As children begin the shift to complementary foods at the end of the exclusive breast-feeding period, their diets may have lacked the requisite nutrients needed to support or sustain neurocognitive development that was gained prenatally (Muthayya et al. 2014, Baldwin et al. 2024).

Another noteworthy finding from the autoregressive model examining changes in scores between 6 and 12 months was that infant sex significantly predicted developmental change, with female infants outperforming males in expressive language. This finding aligns with findings from a study in rural Gambia where females tend to outperform males on the same MSEL expressive language domain (Milosavljevic et al, 2019). In general, however, infant sex was not a consistent predictor of change in any of the other MSEL domains, both between 2- and 24-weeks, and between 24- and 52-weeks., Lastly, infant stunting predicted change in motor development between 24 to 52 weeks. This finding is supported by research that has shown that infant stunting impedes motor development due to symptoms of depleted muscle and fat (WHO, 2006). However, given the negative effects stunting has been shown to have in many areas of development (WHO, 2006), we would have expected it to be a more significant factor in our results. Nevertheless, that stunting significantly predicted gross motor development between 24 to 52 weeks and not between 2- and 24-weeks points to the likelihood that our thiamine

supplementation likely needs to start earlier than the immediate postnatal period, possibly even prenatally.

In sum, despite our initial hypotheses, this study's primary analyses did not yield consistent support for the panel of child and demographic predictors selected to explain the fall-off in several MSEL domains after our trial ceased. Specifically, we were unable to identify systematic child or demographic predictors that could reliably explain the observed changes in infants' MSEL score—particularly the decline in language developmental domains between 6 and 12 months of age. This lack of predictive clarity highlights the complexity of post-supplementation development and suggests that other, unmeasured factors may be contributing to these patterns. One potential explanation for the observed decline, especially in language-related domains, is that the duration of thiamine supplementation may have been insufficient. The falloff in scores may reflect an underappreciation of the metabolic demands required to support emerging language systems during the critical developmental window after 6 months. This possibility is further supported by the broader nutritional context in Cambodia. As infants transition to complementary feeding around six months, dietary diversity and nutrient adequacy may fall short—particularly due to common reliance on parboiled rice, exposure to thiamine antagonists (e.g., betel nut, thiaminase-rich fish), and limited access to thiamine-rich foods. These contextual factors likely compounded the challenge of sustaining neurocognitive gains in the absence of continued supplementation.

An alternative explanation for the fall-off in language MSEL scores between 6- and 12-months could be attributed to cultural differences in the way Cambodian caregivers interact with their infants verbally. Using Prado and colleagues (2014) research on nutrition and early brain development, evidence suggests that cognitive development is reliant on environmental

stimulation in tandem with nutritional adequacy. Environmental stimulation is defined by the level of verbal and physical interaction infants receive (Prado et al. 2014; Rakesh et al. 2024). In the absence of adequate environmental stimulation, infants may be vulnerable to poor developmental outcomes. Poor nutrition and poor stimulation may create additive effects, with infants being impacted by both risk factors (nutrition deficiency & low stimulation) and then subsequently, performing more poorly on measures of cognitive development relative to more stimulated and properly nourished children (Prado et al. 2014). From this study and others, we know that the nutritional context in Cambodia often places infants at risk for nutrient deficiencies during development, which was the basis for the present RCT of thiamine supplementation (Whitfield et al. 2019). It seems reasonable to infer that some infants experienced a cognitive decline after thiamine supplementation ended, likely due to changes in their nutritional status once the supplementation ceased and to the shift at six months postnatally to complementary feeding. However, the results revealed a puzzling pattern: even infants in the placebo group, who had not received thiamine as part of the RCT, showed developmental gains in standardized language scores until 6 months, and then showed declines in these same domains between 6- and 12-months. This suggests that even without the protective effects of thiamine—and following the discontinuation of the intervention at 6 months—infants' language scores in all treatment groups were still noticeably affected. Why did the standardized language scores of a majority of infants fall-off after 6 months, including those who had not previously benefited from supplementation due to their randomization to the placebo condition?

Considering the tandem influences of nutritional adequacy and environmental stimulation on development, the fall-off for all treatment groups (0, 1.2, 2.4, and 10mg/daily) suggests that both risk factors might be influencing the language outcomes seen in the present study. For

infants in the supplementation groups, especially the 10 mg group, the decline in standardized MSEL language scores may be attributable both to the cessation of thiamine supplementation and to under-stimulation to an important period of language impute from caregivers. Infants in the placebo, in contrast, while also subject to nutritional deficiencies associated with the switch to complementary feeding at six months, may also have been impacted by less-than-optimal stimulation. A social engagement task was used to measure mothers' interactions with their infants in the present study may hold clues. Anecdotally (D. Baldwin p.c.), it has been noted that many caregivers seem to use reduced verbal interactions with their infants during engagement tasks. Data on the social engagement task, specifically verbal interaction, may shed light on why infants' language scores dropped for all treatment groups after 6 months.

Study Limitations

In addition to the larger concerns about the duration of our supplementation trial, several other limitations should be considered when interpreting the results of this study. First, while the study aimed to identify demographic predictors of neurodevelopmental change over time, autoregressive analysis may not have fully captured the complex and interacting influences of each variable on early cognitive development. In a low-resource setting such as Cambodia, the predictive power of single variables, such as household income and parental education, may be context-dependent and less informative in environments where access to health, education, and nutrition resources is broadly limited, regardless of income or education level.

Secondly, our models revealed inconsistent associations between predictors and outcomes across MSEL developmental domains and time points. Infant sex and stunting predicted changes in some domains but not others, and only during the 6 to 12-month window.

These isolated findings, while interesting, lacked consistency across subscales and time intervals, limiting their broader interpretability.

Third, the study's design did not include repeated direct measurements of dietary intake of mothers or infants. As a result, we were unable to assess the extent to which the post-supplementation dietary intake of thiamine met developmental needs. Given the known dietary risks in the region—including the use of thiamine-antagonistic foods and low dietary diversity—it remains plausible that inadequate thiamine intake post-supplementation contributed to the decline in language scores observed between 6 and 12 months. This may play a role in the analysis of data as maternal milk thiamine levels at 2 weeks significantly predicted early growth in language and fine motor development. Yet, this association did not persist beyond the supplementation period, suggesting that the advantage conferred prenatally and detectable at 6-months were largely gone or undetectable by one year postpartum.

All together, these limitations underscore the complexity of infant development and the challenges of identifying single-factor predictors for changes over time in neurocognitive outcomes. They also point to the need for more comprehensive, longitudinal, and context-sensitive approaches to studying the long-term effects of early nutritional interventions.

Future directions

For future studies to effectively address the study's original research question—namely, what caused the decline in infants' language scores—we would need detailed data on maternal dietary intake at 2, 24, and 52 weeks, along with information on infants' complementary feeding practices. Access to dietary information would allow for a more accurate assessment of thiamine exposure and intake across critical developmental periods. In addition, extension of thiamine supplementation beyond 6 months allows for greater generalizations surrounding the impact of

maternal thiamine supplementation during the transition to complementary feeding. Continued research that incorporates biochemical and dietary intake data from both mothers and infants—alongside assessments of the developmental impact of thiamine supplementation—will be essential to identifying effective, targeted strategies to prevent thiamine deficiency in regions where dietary diversity is limited. A longitudinal study extending to 24 months is vital to investigate the benefits of thiamine supplementation during periods where the recommended daily intake of thiamine continually increases for infants. It is important to note that the first 2 years require adequate thiamine intake to attain proper developmental trajectories as seen in cases of detrimental thiamine deficiencies in infancy impacting children well into late childhood (Whitfield et al., 2017). This reinforces the need to extend thiamine-focused intervention and monitoring of potentially influential dietary constraints throughout this critical period.

As mentioned in the explanation of results, environmental stimulation may be a factor contributing to the fall-off in standardized language scores after 6 months. Environmental stimulation facilitates infant engagement and learning (Rakech et al., 2024). Without consistent verbal stimulation, infants may not be verbally engaged enough to continue making gains in receptive and expressive language, at least relative to North American infants where considerable emphasis is placed on early cognitive stimulation (Richman et al., 1992). The reduced verbal interactions noted by our team of researchers in the present study may point to cultural differences between U.S. and Cambodia caregivers, one that could partly explain the decline in standardized scores after 6 months. It is worth noting, however, that when examining the raw scores alone, Cambodian infants continued to show growth in expressive and receptive language. Interestingly, both gross and fine motor scores increased across raw and standardized metrics, with motor development increasingly aligned with U.S. norms. This raises questions: Is

motor development more culturally prioritized for Cambodian infants? Is language development a secondary outcome due to lifestyle demands? In rural Cambodia, where agriculture plays a central societal role, parents may naturally emphasize physical activity and environmental exploration (Prado et al 2014; NIS et al. 2023). These findings suggest that cultural practices and environmental priorities, such as an emphasis on physical development over verbal interaction, may influence how Cambodian infants progress in different developmental domains, highlighting the limitations of using U.S.-based standardized measures to assess global developmental trajectories. Given such cultural considerations, future studies that use measures such as the MSEL would benefit from comparison samples that may be more similar to the Cambodian contest, for example, other SE Asian countries.

Conclusion

The central aim of this study was to investigate whether child and demographic factors could explain the decline in infants' language scores following maternal thiamine supplementation. We did so by assessing the influence of demographic variables in predicting change in developmental outcomes using scores on the Mullen's Scale of Early Learning from one time point to the next (2- to 24 weeks, and 24- to 52 weeks). While early breast milk thiamine levels predicted developmental gains at 6 months, these effects did not persist after supplementation ended. Demographic variables showed limited and inconsistent predictive power, and the decline in language scores between 6 and 12 months remains largely unexplained.

These findings highlight the importance of sustained thiamine intake beyond 6 months, particularly as infants transition to complementary feeding, while their nutritional needs increase.

Future research should include longitudinal tracking of maternal and infant dietary intake, extended supplementation, include SE Asian cultural comparison samples, and broader contextual data to better understand and support neurodevelopment in resource-limited settings.

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