BAYLEY SCALES OF INFANT DEVELOPMENT III AND MULLEN SCALES OF EARLY LEARNING IN NUTRITION AND SUPPLEMENT STUDIES: A PILOT SYSTEMATIC REVIEW

by

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Thiamine (vitamin B1) is a micronutrient essential to both metabolic functioning and development. It helps the body to take energy from the nutrients it takes in. Due to a diet heavily reliant on polished white rice in some areas of the world like Cambodia, deficiency is common. This can affect brain and cognitive development in children and even become a life-threatening medical emergency. A new clinical trial in the design phases aims to test the efficacy of preventing thiamine deficiency at the population level by fortifying salt with thiamine, as is done with iodine. My thesis provided a pilot systematic review to assist in the design of this new clinical trial. The pilot review focused on two neurocognitive tasks, the Bayley Scales of Infant and Toddler Development III (BSID III) and the Mullen Scales of Early Learning (MSEL). I analyzed the available evidence in a pilot subset of published articles regarding the effectiveness of these two tasks for measuring cognitive effects in nutrition studies. Inclusion criteria included nutritional research and neurocognitive studies involving the two tasks that took place in lower- and middle-income countries. The participants were between infancy and age 5, and articles were published between 2013-2023. Of the 657 articles resulting from a search of APA PsyNet and PubMed, twenty-one articles were selected for review, involving 25,486 infant participants.

The majority of selected studies showed neurodevelopmental effects using either the MSEL or BSID III. Limitations included a lack of assessment of bias within articles and involvement of just one coder. The results of the pilot review showed that both MSEL and BSID III tasks appear to be sensitive to nutrition-related neuro-cognitive effects in infants and toddlers in lower- and middle-income countries.

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Table of Contents

List of Figures and Table

Introduction

Thiamine, also known as vitamin B1, is an important micronutrient to human health and is vital to human development. It is involved in the generation of energy from other nutrients (World Health Organization, 1999). Due to its short half-life, the body relies heavily on a dietary intake of thiamine (Whitfield et al., 2018). It is found in legumes, whole grains, meats and nuts, and in many high-income countries, cereals and flours are fortified with thiamine (Whitfield et al., 2018).

In Southeast Asian nations such as Cambodia, thiamine deficiency is unfortunately common (Whitfield et al., 2017). The local diet, which mainly consists of polished white rice and fish, contributes to the persistent problem of thiamine deficiency (Chan et al., 2021; Whitfield et al., 2017). Clinical levels of deficiency can result in a medical emergency called infantile beriberi, which can be fatal if not promptly treated. Moreover, growing evidence indicates that even subclinical levels of thiamine deficiency in infants can impact neurological and cognitive development (Fattal-Valevski et al., 2005; Fattal-Valevski, et al., 2009). In particular, Fattal-Valevski and colleagues (2009) compared 20 Israeli infants whose early-life diet was lacking in thiamine due to an inadvertent manufacturing error to 20 infants fed typical milk sources. Subsequently, infants fed the thiamine-deficient formula displayed significant neuro-cognitive delays, especially in language development.

A recent clinical trial investigated the efficacy of supplementing thiamine for lactating mothers in Cambodia, where thiamine deficiency is unfortunately common (Whitfield, et al., 2015), to protect their infants' health, growth, and neuro-cognitive development. Mothers received daily thiamine capsules from 2 weeks to 24 weeks after giving birth. Mothers were randomly assigned to receive capsules containing either 0 mg, 1.2 mg, 2.4 mg, or 10 mg of thiamine each day (Gallant et al., 2021). Because these infants were breastfeeding, they were receiving supplemental thiamine via their mothers' breast milk. In addition to a variety of biological (e.g., infant and maternal blood and maternal breast-milk samples) and anthropometric (e.g., weight, length, head circumference) measures, infants participated in several neuro-cognitive tasks at 2 weeks, 12 weeks, and 24 weeks, as well as at a 52-week follow-up (six months after thiamine supplementation ended) to evaluate various aspects of neuro-cognitive development. Among these, the Mullen Scales of Early Learning (MSEL) were assessed at each of these ages. The MSEL was administered by trained staff and was used as a standardized test for assessing gross motor, fine motor, visual reception, receptive language, and expressive language abilities (Measelle et al., 2021). In this clinical trial, thiamine supplementation levels significantly and positively predicted infants' receptive and expressive language scores on the MSEL, but, by and large, no significant impact was observed on the other three MSEL domains (gross motor, fine motor, visual reception) (Measelle et al., 2021). As well, maternal thiamine supplementation levels in this clinical trial displayed a dose-response relationship to infants' facility at language processing, as measured by the magnitude of their preference for infant-directed relative to adult-directed speech (Baldwin et al., under review). Together, these findings regarding benefits of maternal thiamine supplementation for language outcomes provided the first experimental evidence to date that availability of adequate thiamine in early life influences infants' neuro-cognitive development.

The team that conducted the research reported in the Measelle et al. (2021) paper plans a future clinical trial in Cambodia examining the efficacy of fortifying salt with thiamine for protecting the populace more generally against thiamine deficiency, thus avoiding negative consequences for children's neuro-cognitive development. One aspect of planning for this clinical trial involves selecting measures of neuro-cognitive development that are sensitive to nutritional and micro-nutrient status and appropriate for use in lower- and middle-income countries (LMIC) in home settings. To assist with this, the present thesis aimed to review recent research involving two neuro-cognitive assessment tools commonly used in nutritional studies to evaluate the neuro-cognitive development of infants and young children. Of particular interest was the extent to which existing findings confirm that the MSEL is well-chosen for monitoring infants' neuro-cognitive development in the context of a fortification trial in a LMIC setting. Specifically, the thesis a) developed the process for a systematic review of existing research comparing use and outcomes related to the MSEL and another commonly utilized neuro-cognitive measure, the Bayley Scales of Infant Development III (BSID III) in nutrition-related developmental studies conducted in LMIC contexts, and b) presented a "pilot" review of 21 studies falling within the larger set of relevant articles.

The systematic review pilot aims to demonstrate the viability of the approach we are taking to systematic review and lay the groundwork for a future comprehensive large-scale review that will inform decision making for the clinical trial of thiamine fortification that is under development. In the following sections, I will briefly review the two neuro-cognitive assessment tools considered in the systematic review pilot, as well as the rationale for designing the systematic review to focus on them. I will then introduce the outlines of the large-scale review and present the rationale for information collected in the small-scale pilot review.

Bayley Scales of Infant Development (BSID III)

The Bayley Scales of Infant Development is a tool used to measure the developmental functioning of infants and toddlers and is used to identify developmental delays and monitor progress in development. The BSID III, published in 2006, is the revision of the Bayley Scales of Early Learning and incorporates significant changes from its predecessors. Notably, the BSID III includes five different scales of developmental assessment including cognitive, motor, language, socio-emotional, and adaptive behavior (Bayley, 2006). The BSID III can evaluate children ages 16 days postnatal to 42 months of age (Baladsundaram, 2022). The most recent revision, the BSID IV, was published in 2019, but was not used in any of the studies available for review in this thesis. Due to the limited translations of this newest revision, it is not yet widely used in nutritional studies in lower- and middle-income countries.

A literature review of neurodevelopmental assessments in LMIC settings found that some studies using the BSID III may show significant differences influenced by cultural or linguistic variations (Semrud-Clikeman et al., 2017). For example, in the case of assessments used in Cameroon, significant differences emerged in the gross motor skills and language domains. Compared to German infants, Cameroonian Nso farming infants were accelerated in their gross motor development in early infancy. However, this difference disappeared between 6 and 9 months of age. A plausible cultural explanation for the accelerated development in gross motor development among Cameroonian Nso infants could be attributed to the cultural norm for Cameroonian children to contribute to errands as soon as they begin to walk (Vierhaus et al., 2011). Notably, there was no significant difference shown between German and Cameroonian infants in fine motor development. This lack of difference may be due to the German infants' higher familiarity with the types of toys and objects utilized in the BSID III. The existing research does not clarify the sources of language differences. The differences may originate from poor adaptation of the test to the cultural or linguistic context, or instead reflect genuine differences in Cameroonian infants' developmental trajectories. Further research is needed to gain increasing clarity on these issues. In any case, these findings indicate that the BSID III is likely sensitive to neuro-cognitive differences related to LMIC versus higher-income contexts for infant development.

The administration time of the BSID III ranges from 30-90 minutes, depending on the age of the child. The score involves both an examiner who assesses the child and a caregiver report. The test can only be administered by those with a master's degree or formal training in fields such as healthcare, psychology, education, speech language pathology, occupational therapy, social work, counseling, or a related field. It is also required to have a certification or membership in a professional organization that provides training in administration of assessments (Bayley, 2006).

The BSID, encompassing all four versions, is the most commonly used test for assessing child development in children aged 1-42 months and has been used in 25 different LMICs. It is commonly considered the most comprehensive global test and often serves as a reference measure for developmental assessments (Frongillo et al., 2014). In addition, the BSID III has demonstrated strong predictive validity of IQ compared to the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) in pre-term children at age 4 (Bode et al., 2014).

However, there are some drawbacks to the BSID III in comparison to other available tests for evaluating child development in LMIC settings. The training qualifications for evaluators and the cost of the test are major considerations. In addition, the test is designed for English-speaking and Western countries, so it must be translated and modified for LMIC settings to appropriately evaluate development (Frongillo et al., 2014).

Mullen Scales of Early Learning (MSEL)

The Mullen Scales of Early Learning (MSEL) is an assessment tool that evaluates five domains of developmental progress: gross motor, fine motor, visual reception, receptive language, and expressive language. It is designed to test children aged 3-60 months (Mullen, 1995). The MSEL provides an "early learning composite" score, derived from four of the five subscales (excluding the gross motor subscale), to evaluate overall development. This assessment was created in 1995 and has not undergone revisions.

The reliability of the MSEL has been studied in LMIC settings; for example, in Benin and Uganda (Semrud-Clikeman et al., 2017). Minimal modifications to the MSEL (other than linguistic translation) were necessary for use in these populations, and the reliability was reported to be good in these specific LMIC settings.

The MSEL takes between 15-60 minutes to complete, depending on the age of the child. It has been used to assess children from birth to 68 months, which means that its application seems to be somewhat more expansive even than the age range for which it was designed (3-60 months). The MSEL has the same administration qualification requirements as the BSID III. Parental reports are not considered for the scoring of the MSEL (Mullen, 1995).

The MSEL is commonly used to identify and quantify developmental delays in children. Its construct validity was tested in its validation study (Mullen, 1995) through studies of convergent and divergent validity. The MSEL's convergent validity, which refers to the degree to which the new test is related to other tests that measure the same or similar constructs, was studied by comparing the MSEL to several other tests including the BSID, and all domains of the MSEL except gross motor showed large correlations with the BSID. The Peabody Fine Motor Scale and Preschool Language Scales were also used to gain evidence regarding convergent and divergent validity of the MSEL. More recently, Swineford et al. (2015) examined the validity of the MSEL in 399 children with and without autism spectrum disorder (ASD). Of particular interest was the extent to which the MSEL displays adequate validity for measuring developmental change in children with autism as well as in neuro-typical children. This was a focus due to concerns that autism symptoms might interfere with MSEL scoring. For example, children with ASD typically experience language delays, and their linguistic deficits might negatively impact their MSEL scores. In any case, however, Swineford and colleagues' findings confirmed construct, convergent, and divergent validity of the MSEL for both ASD and neuro-typical children, while also indicating that MSEL scores of ASD children are not informative about their degree of ASD symptomatology itself.

Similar to the BSID III, the drawbacks to the MSEL include the qualifications required of evaluators and cost of the test. Similarly, the test was written in English and for children in Western countries and must therefore go through language and cultural adaptation for use in LMIC settings. Evidence of reliability in both LMIC and higher-income settings is a benefit to using the MSEL.

Comparing the BSID III and MSEL

Both the BSID III and MSEL provide researchers with a composite score that measures children's developmental progress as well as separate scales for evaluating children's functioning in specific domains. While both measure language domains and motor domains, the BSID III has a more general evaluation of motor and language domains, whereas the MSEL offers individual scales for both fine and gross motor domains and expressive and receptive language domains.

The relative breadth of the age span appropriate for testing (birth to 68 months) is one advantage of the MSEL, given that the BSID III is limited to 1-42 months (Semrud-Clikeman et al., 2017). However, the MSEL has not been recently updated since its initial publication in 1995, while the BSID III was revised in 2006, with a newer version, the BSID IV, published in 2019. However, the utilization of the BSID IV remains limited in LMIC settings (Semrud-Clikeman et al., 2017).

Both assessments require the same level of qualification to conduct the assessment. Both assessments were also created to represent the US population instead of populations specifically in LMIC settings, but have been adapted to various LMIC settings and into some other languages. When the MSEL was used in LMIC settings, it was found to require minimal modifications. Both the MSEL and the BSID III appear to be sensitive to potential developmental differences in children growing up in LMIC settings compared to high-income settings.

Despite abundant research on both the BSID-III and MSEL regarding their use in monitoring early development, a thorough comparison between the two tasks and their use in nutritional studies in lower- and middle-income countries has not yet been undertaken. Assessing the use of the BSID III and MSEL in nutritional studies, micronutrient supplementation studies, and in LMIC contexts will enable analysis of the patterns in their use and outcomes. More specifically, a systematic review is needed to evaluate the extent to which the BSID III and MSEL reveal significant relationships between nutrition or micro-nutrient status and early neuro-cognitive functioning, with particular focus on LMIC contexts.

Outline of the Large-Scale Systematic Review

As described earlier, the present thesis was a pilot study for a large-scale systematic review aiming to analyze the existing literature utilizing the BSID III or the MSEL in nutritional and micronutrient deficiency studies, specifically taking place in LMIC. The proposed large-scale review will involve searching various databases, including PubMed, APA PsycNet, Web of Science, and Google Scholar, using search terms such as “BSID III,” “MSEL,” “micronutrient,” “nutrition,” “nutrient deficiency,” “micronutrient supplement,” “malnutrition,” “LMIC,” and the list of countries considered LMIC. The review should ideally include a similar number of articles that use the MSEL and BSID III to measure neuro-cognitive development.

The information to be collected from the selected articles will include the publication year, the country and the income level of the country, and the type of study. Data regarding the sample will be collected, including the number of children, and, if applicable, the number of parents involved in the study, and the age of the children. If biomarkers were measured, details about the specific biomarkers measured and at what age they were assessed will be recorded. The usage of the BSID III or MSEL, along with the age at which they were administered, will also be documented. Furthermore, scores in specific domains measured and the composite score (if reported) will be recorded. In cases where a treatment or intervention was implemented, specific details about the intervention will be noted, and any correlations between the neuro-cognitive assessment and treatment will be recorded. The effect sizes will also be documented.

The large-scale review will involve multiple researchers searching these databases for relevant articles and coding specific data points within the selected articles. The review will adhere to the PRISMA guidelines, which provide a protocol that guides systematic reviews and their reporting (Page et al., 2021).

Purpose of the Small-Scale Pilot of Systematic Review

A small subset of articles was chosen for this small-scale pilot review, including a subset of 21 relevant articles. Two databases were searched, PubMed and APA PsycNet. The review was conducted by a single researcher following the PRISMA protocol. The information coded in the pilot review included the same criteria as listed above for the large-scale review, with the exception of effect sizes, which were not included in the data collection.

The small-scale pilot review served as a trial run, providing an opportunity to assess the number of articles utilizing the BSID III or MSEL in nutritional research in LMIC contexts. It played a crucial role in refining the selection criteria for articles, determining specific search terms, and identifying appropriate databases to search in the larger review. Additionally, it helped to identify the specific information to be extracted from selected articles.

Method

The central aim of this systematic review pilot was to provide a small-scale, initial attempt to evaluate neuro-cognitive outcomes emerging from nutrition and micronutrient supplement studies that utilized the BSID III and/or the MSEL. To do so, we a) established literature search criteria to guide which studies to include in the review, and b) developed a system to codify relevant characteristics of each selected article in relation to dimensions such as the type of study conducted, the measures (and sub-scales) utilized, and the nature of the findings.

Criteria for Considering Studies for Review

Types of Studies

To guide the selection of studies for the review, we limited the inclusion to randomized controlled trials, observational studies, and prospective cohort studies. Only completed studies published in scientific articles and only articles with full texts were considered.

Exclusion Criteria

We excluded studies that evaluated the developmental impact of exposure to illness, teratogens, or antiretroviral medications. We also excluded studies that used the BSID 1st or 2nd edition due to changes from the 2nd to 3rd edition that made the 3rd edition more comparable to the MSEL. Articles reporting case studies, validation studies, and systematic reviews were also excluded.

Search Strategy and Terms

I searched PubMed and APAPsycNet, with the final search occurring on April 14, 2023. To ensure relevance, we applied a 10-year publication date range from 2013-2023 and an age filter of infancy through 5 years.

Regarding search terms, I looked for studies that measured or tracked micronutrient status or nutritional status in LMIC settings. The compilation of LMIC countries was drawn from the 2021 World Bank dataset. Several articles selected for review took place in upper-middle income countries and higher-income countries, as defined by the World Bank 2021 criteria. Additionally, these studies needed to focus on neuro-cognitive development and utilize either the BSID III or MSEL.

The terms "Mullen Scales of Early Learning" and "Malnutrition" or "Supplementation" guided the article search. The same search was used for the BSID III, by searching "Bayley Scales of Early Learning" and "Malnutrition" or "Supplementation." The other search pathway involved "Bayley Scales of Early Learning" and a list of lower and middle-income countries, as defined by the World Bank, on the one hand, and, on the other hand, the "Mullen Scales of Early Learning" and the same list of LMIC countries (World Bank Open Data, n.d.).

Review of Articles

For the review of articles, I initially reviewed the article abstracts to determine if they met the inclusion criteria. If necessary, I reviewed the whole study with a focus on the methods and results to determine if it fit our inclusion criteria. I served as reviewer for screening every report, and two additional reviewers (Advisors Baldwin and Measelle) were consulted to assist in screening several studies to ensure the inclusion criteria were met. The selected group from this method contained too many articles for inclusion given the available timeframe, so the final set of articles for full review was determined based on those receiving the highest level of citations (according to Web of Science citations) to extract the most influential articles in the group. This method yielded a final set of 21 articles for review in the pilot.

Data Collection and Analysis

Data collection and analysis involved recording the type of study, the presence of an intervention and placebo control, age range of participants, the age of the neuro-cognitive test, baseline data on biomarkers, and measurements of micronutrient levels. For studies with interventions, we tracked neuro-cognitive measures, biomarker measurements, and treatment effects on micronutrients levels and neuro-cognitive status (See Table 1).

For all studies, we considered whether there was an association between nutrition and neuro-cognition. We also took note of whether the researchers used any additional neuro-cognitive measures.

Table 1

Coding Categories for Articles Selected for Review

Coding Category	Purpose of Coding Category
Author, Title, Publication Date	
Location of study	To assess income level of country where the study took place.
Mother sample size	Specify the number of mothers involved in the study, if applicable.
Baby sample size	Specify the number of babies or children in the study.
Type of study	Determine whether the study was a randomized controlled trial, observational, or longitudinal.
Intervention study	Indicate whether the study involved an intervention.
Placebo Group	Indicate whether a placebo group was used in the study.
Age Range of Study	Note the age range of the children in the study.
Age of Intervention	Note the age range during which an intervention was implemented.

Age of Test	Record the ages at which the child was assessed with the BSID III or MSEL.
Baseline Biomarkers, Neuro-Cognitive Measures, and Micronutrient Levels	Specify whether baseline biomarkers, neuro-cognitive measures and micronutrient were assessed was noted, and indicate which micronutrients were measured.
Treatment Effect on Micronutrient Status	Indicate whether the study measured treatment effects on micronutrient levels if applicable.
Association Between Nutrition and Neuro-Cognitive Status	Indicate whether the study found an association between nutrition and neuro-cognitive status.
Treatment Effect on Neuro-Cognitive Status	Indicate whether the treatment had an effect on the neuro-cognitive status if applicable.
Additional Neuro-Cognitive Measures	Indicate if additional neuro-cognitive measures were used and specify which ones.
Type of Neuro-Cognitive Effect	Indicate the type of effect: cognitive, language (receptive or expressive), motor (fine or gross), or composite, as measured by the MSEL or BSID III. Indicate which groups the effects were associated with (placebo or intervention groups or dose response).
Neuro-Cognitive Effect on Multiple Domains	Indicate if a neuro-cognitive effect measured on multiple domains.
Test that Showed Effect	Indicate whether the BSID III or MSEL showed the neuro-cognitive effect.
Thiamine measured	Indicate if thiamine was used in micronutrient intervention or measurements.

Synthesis and Analysis

Synthesis and analysis included grouping studies by type, neuro-cognitive test used, and presence of an intervention. In studies that found a neuro-cognitive effect, I noted the type of neuro-cognitive effect, affected domains, and the specific test used to show the effect. Associations between treatments and test outcomes, including dose responses, were noted.

Missing Data and Limitations to the Pilot Systematic Review

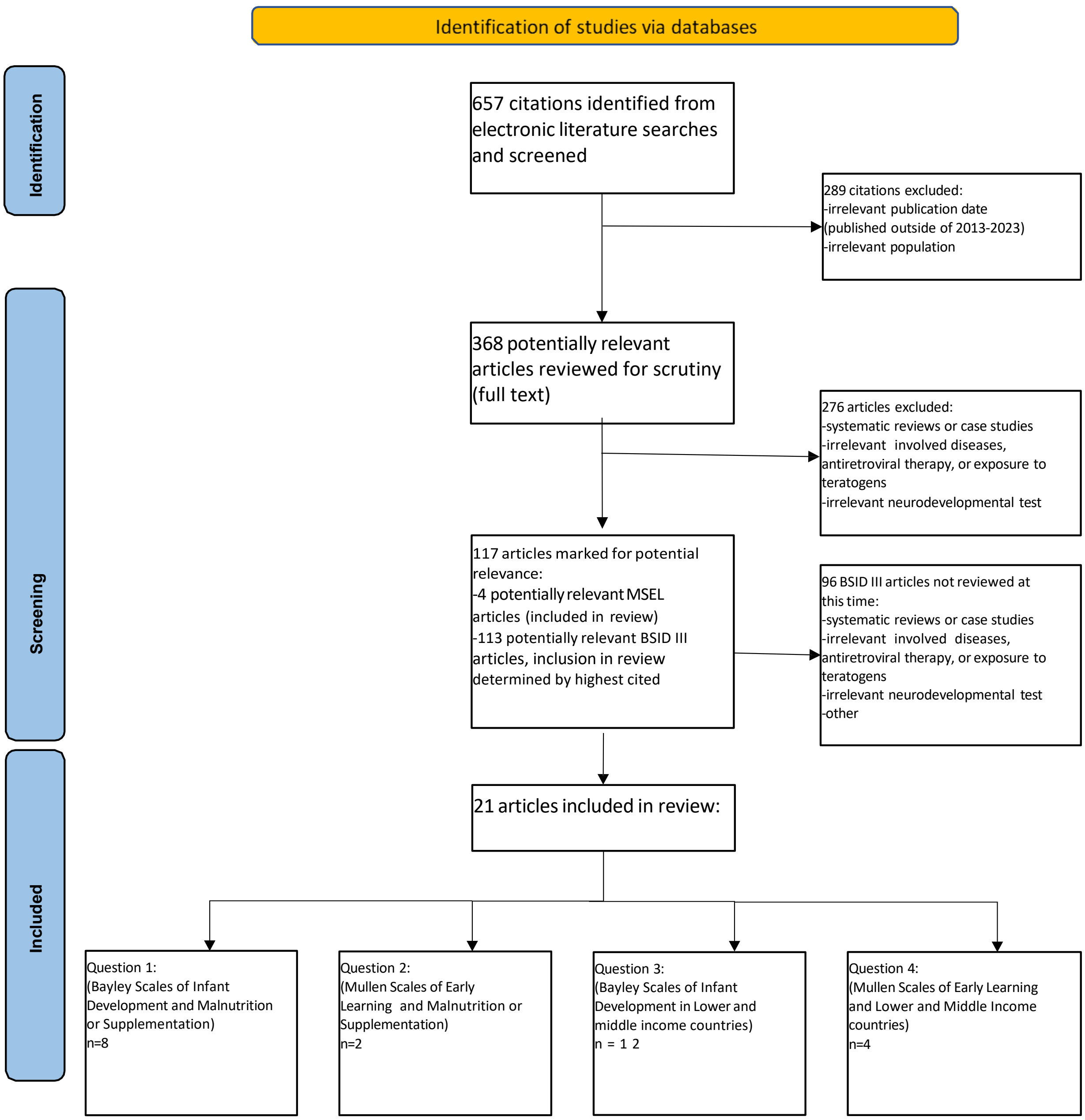
Missing data were recorded in the coding process. Methods to assess risk of bias were not used in this literature review. Furthermore, only one reader reviewed the majority of articles to be included or excluded, as well as coding the data from each included article.

Results

The search process initially identified 657 citations in total, from the four searches. Two hundred eighty-nine articles were excluded from the selection set after filters were placed on the searches. Filters included age filters from infancy to age 5, and publication date from 2013-2023. Three-hundred-sixty-eight articles were scrutinized in full, which included reviewing the title, abstract, and if necessary, the full text. Two hundred seventy-six articles were excluded from this set if they were case studies or systematic reviews, involved exposure to disease, antiretroviral therapies, or teratogens, or tested neurodevelopment without using the BSID III or MSEL. One hundred and seventeen articles qualified for potential relevance, with four utilizing MSEL and 113 utilizing the BSID III. Due to this literature review only having one reviewer, the set was further narrowed by using the Web of Science "most cited" feature to select the most influential and cited BSID III articles. The final set included 21 articles. Several articles were found through more than one search, and therefore overlapped in the search process. Figure 1 below encapsulates the process of identifying selected articles for review.

Figure 1.

The Search and Selection Process of Retrieved and Selected Articles



Note. *Some articles were found in more than one search and are counted more than once

Summary of Selected Articles

Mulder et al. (2014) conducted a randomized controlled trial involving fetal DHA (docosahexaenoic acid) and DHA deficiency on central nervous system development. The study used the BSID III to measure development and found that the placebo group had lower language development and visual acuity.

Singla et al. (2014) used the BSID III to evaluate the cognitive and language development of infants in a randomized controlled trial involving a daily multi-micronutrient powder intervention. The intervention had a significant effect on expressive language but not the other domains of the BSID III.

Yousafzai et al. (2014) conducted a randomized trial including interventions such as micronutrient powders, nutrition services, and nutrition education in Pakistan. Children who received responsive stimulation had higher scores on cognition, language, socio-emotional, and motor scales; no added benefits on cognition for the enhanced nutrition intervention were found but the children with enhanced nutrition had improved height for age scores.

Manji et al. (2014) conducted a randomized controlled trial including a placebo control to study the effect of multivitamins on infant development of infants exposed to HIV in utero. The multivitamins did not have a significant effect on any scales of the cognitive development, measured by the BSID III.

Attanasio et al. (2014) studied the use of psychosocial stimulation and micronutrient supplementation on infant development in a randomized controlled trial in Colombia. While stimulation improved cognitive scores and receptive language scores using the BSID III, micronutrient supplementation had no significant effects on any development scores.

Sudfeld et al. (2015) used the BSID III to measure the effects of malnutrition and its effects on cognitive development on Tanzanian infants previously enrolled in a vitamin A supplementation trial. The results found that higher height for age scores were associated with higher scores in cognition, communication, and motor development.

Mireku et al. (2015) measured the impact of maternal anemia during pregnancy on infant development in a prospective cohort study in Benin. Using the MSEL, researchers found that the infant gross motor scores improved with higher maternal hemoglobin levels until a certain concentration (90 g/L), and gross motor scores decreased when maternal hemoglobin levels exceeded 110 g/L.

Christian et al. (2016) used a randomized controlled trial to measure the effects of pre- and postnatal multiple micronutrient supplements to infants and on cognitive development. Using the BSID III, this study found no cognitive or motor effects of supplementation, but the supplementation improved length for age scores and reduced stunting.

Mireku et al. (2016) measured the impact of maternal iron deficiency on infant development using a prospective cohort study. Prenatal iron deficiency was not associated with poor cognitive or motor function of infants as measured by the MSEL.

Jiang et al. (2017) studied markers of inflammation such as C-reactive protein and soluble CD14 and their association with neurodevelopmental scores on the BSID III in Bangladesh. The study found that with higher levels of sCD14, cognitive and motor scores were lower at 78 weeks and in all domains of BSID III at 104 weeks.

Nguyen et al. (2017) studied the impact of prenatal multiple micronutrient supplements in Vietnam on infant cognitive development. This randomized controlled trial found that supplementation that included iron and folic acid improved infant growth and motor development as measured by the BSID III.

Berglund et al. (2017) also studied the impact of maternal iron deficiency and being overweight on infant development using the BSID III. Maternal iodine deficiency was associated with lower motor, language and cognitive scores.

Nguyen et al. (2018) studied the impacts of nutritional status on cognitive development in Vietnam and found that stunted children scored lower than non-stunted children in cognition, language and motor development as measured by the BSID III.

Markhus et al. (2018) studied the impact of maternal iodine deficiency and the impact of maternal iodine supplementation on infant development. While maternal iodine was associated with lower language skills and no other domains of the BSID III, maternal use of iodine supplements was associated with lower gross motor skills and no other domains of the BSID III. This is the only study in the reviewed articles which found a negative association between a nutritional supplement and cognitive development scores.

Blakstad et al. (2019) measured the association between maternal and infant nutritional status and infant development using the BSID III in Tanzania. Higher length for age scores of the infant predicted higher cognitive and language scores.

Khandelwal et al. (2020), in an observational study, measured the development of children with severe acute malnutrition in India, and found that children with severe acute malnutrition had delays in the motor, language and cognitive domains of the BSID III.

McCormick et al. (2020) used an observational cohort to evaluate early life experiences such as infections and malnutrition on a child’s developmental trajectory. Using the BSID III, the researchers determined that higher quality diet yielded higher cognitive scores among other factors.

Black et al. (2021) used the BSID III to measure cognition in preschool aged children in India who received a multi-micronutrient powder intervention or a placebo group. The researchers found the micronutrient powder had positive effects on expressive language and socioemotional domains in children in low quality preschools, and the intervention also reduced anemia and iron deficiency.

Sudfeld et al. (2021) studied the use of community health worker interventions and conditional cash transfers (a program for which cash transfers are conditional upon use of health services) on child development in a randomized controlled trial in Tanzania. Both the intervention using community health worker and cash transfers and just cash transfers yielded higher child cognitive development scores compared to the control group, measured by the BSID III.

Measelle et al. (2021) studied the impact of maternal thiamine supplementation on breastfed infants' development in Cambodia through a randomized controlled trial. Using the MSEL, thiamine supplementation was found to hold significant benefits on language scores.

Tran et al. (2023) used a randomized controlled trial to measure the cognitive effects of preconception micronutrient supplementation as measured by the BSID III. Significant wealth gaps were found in cognitive development, child nutritional status mitigated the wealth gaps in cognitive development.

Descriptive Information of Selected Studies

Of the included studies, 16 (80%) took place in low- and middle-income countries, while 1 (5%) took place in an upper-middle income country and 3 (15%) took place in higher-income countries. In total, the studies took place in 14 different countries.

The selected studies had 25,486 infant participants in total. The infant participants had a total of 100-8,529 and a mean of 1,214. The total number of maternal participants was 21,992; 6 of 21 studies did not use maternal data. The maternal participants ranged from 270-8,529, with a mean of 1,466.

As a whole, the studies included had an infant participant age range at study onset between preconception to third year postnatal. Two (10%) of the studies began preconception, 7 (33%) began prenatally, 10 (48%) began at birth or in the first year postnatal, 1 (5%) began in the second year postnatal, and 1 (5%) began in the third year postnatal. The infant participant ages at the conclusion of the studies ranged from birth or first year postnatal to fifth year postnatal or older. While 19% of studies included ended by birth or first year postnatal, 11 (52%) ended second year postnatal, and 3 (14%) ended fifth year postnatal or older. One (5%) ended third year postnatal, and one (5%) ended fourth year postnatal. See Table 2.

Table 2

Age of Child Participants Throughout Selected Studies

Child Age of Study	**Start of Study (%)**	**n=**	**End of Study**	**n=**
Preconception	10	2	0	0
Prenatal	33	7	0	0
Birth/First year postnatal	48	10	19	4
Second year postnatal	5	1	52	11
Third year postnatal	5	1	5	1
Fourth year postnatal	0	0	5	1
Fifth year+ postnatal	0	0	14	3

Study Design

Of the reviewed articles, three types of studies were included: randomized controlled trials, observational studies, and prospective cohort studies. Thirteen (62%) of the studies were randomized controlled studies, while 4 (19%) were observational and the remaining 4 (19%) were prospective cohort studies.

Study design varied among the reviewed studies, with 16 (76%) of studies involving an intervention. The remaining 5 (24%) were non-intervention studies. Twelve (67%) studies included a placebo condition. Six (33%) studies did not include a placebo control. As is apparent in Table 3, intervention studies differed considerably in the period within infant development that was examined, with the largest group of studies (25%) focusing on infants between the first and second year postnatal.

Table 3

Child Participant Age During Intervention

Child Age during Intervention	Intervention Period (%)	n=
Preconception to birth	19	3
Prenatal to birth	6	1
Prenatal to first year postnatal	13	2
Prenatal to second year postnatal	13	2
Birth through first year postnatal	13	2
First year to second year postnatal	25	4
Second year through third year postnatal	6	1
Entirely fourth year postnatal	6	1

Also of interest was the breakdown in terms of which neuro-cognitive measures were utilized across the 21 articles to monitor infants' neuro-cognitive development. The BSID III was utilized by substantially more articles than the MSEL. Eighty one percent (17/21) of the articles used the BSID III to measure neuro-cognitive status while the remaining 19% (4/21) used the MSEL. Four (19%) articles utilized an additional test of some kind to measure neuro-cognition.

Articles also differed in terms of inclusion in the research of baseline measures and a placebo control group. Seventy-five percent of intervention studies in total utilized a placebo group, while 81% measured biomarkers. Just 57% of intervention studies utilized both a placebo group and baseline biomarkers. Table 4 highlights that biomarker baseline measures were common, but micro-nutrient and neuro-cognitive baseline measures were much less so.

Table 4

Biomarker, Micronutrient and Neuro-cognitive Measures Collected

Baseline Measures Collected	**Frequency**	**%**
Biomarker baseline	17/21	81
Micronutrient baseline	9/20	45
Neuro-cognitive baseline	6/21	29
Intervention	**Frequency**	**%**
Biomarkers measured (child)	18/21	86
Biomarkers measured (mother)	1/21	5
Micronutrient measured before intervention	7/16	44
Neuro-cognitive measures taken (child)	18/21	86

Another aspect of the selected studies of interest was the usage of placebo groups in intervention studies and the measurements of biomarkers at baseline, and in particular any patterns with neuro-cognitive assessment used. Both studies that used the MSEL as the assessment tool for the intervention studies but did NOT use a placebo group were prospective cohort studies. Both studies that used the BSID III as the assessment tool for the intervention study but did not use a placebo group were randomized controlled trials. Three of 4 articles that used the BSID III in their intervention study but did not take baseline biomarkers were randomized controlled trials; the remaining one was a prospective cohort study.

Among the reviewed studies, only 33% included assessments of neuro-cognition at the baseline stage. Notably, a higher proportion of studies that used the MSEL assessed neuro-cognition at baseline compared to studies which utilized the BSID III. See Table 5.

Table 5

Frequency of Placebo Groups in Intervention Studies, Baseline Biomarkers, and Neuro-Cognitive Measures by Neuro-Cognitive Assessment

Neuro-cognitive Assessment Used	Placebo Group Used	Baseline Biomarkers Taken	Both Baseline and Placebo Used	Baseline Neuro-Cognitive Assessment
MSEL	50% (2/4)	100% (4/4)	50% (2/4)	50% (2/4)
BSID III	83% (10/12)	76% (13/17)	59% (10/17)	24% (4/17)

Neuro-cognitive Effects Measured

Of the neuro-cognitive effects observed, 18 studies (86%) found a statistically significant association between nutrition and neuro-cognitive measures. Of intervention studies, 12 out of 16 (75%) found a treatment effect on the neuro-cognitive status of the child. Of the articles which found a significant association between nutrition and neuro-cognitive measures, 17 found an exclusively positive association.

The MSEL showed effects in 3 (75%) of the studies involving the MSEL, 2 of which were exclusively positive. The BSID III showed effects in 14 (82%) of the studies that used the BSID III; all were positive associations between the effects and cognitive development. In sum, nutritional interventions displayed statistically significant relationships to neuro-cognitive development when measured by both the MSEL (75%) and BSID III (82%).

Of the randomized controlled trials, 11 (85%) found an association between nutrition and neuro-cognitive status. Of the observational studies, 4 (100%) found an association between nutrition and neuro-cognitive status. Of the prospective cohort studies, 3 (75%)

found an association between nutrition and neuro-cognitive status.

Of the intervention studies, 13 (81%) found an association between nutrition and neurocognitive status. In non-intervention studies, 5 (100%) found a positive association between nutrition and neuro-cognitive status.

As can be seen in Table 6, the vast majority of studies reported significant associations between nutrition and neuro-cognitive status, with nearly all those in the predicted positive direction.

Table 6

Neuro-cognitive Outcomes Observed

Neuro-cognitive Outcomes observed	**Frequency (%)**	**Only Positive Association (%)**
Association between nutrition and neuro-cognitive measures	18/21 (86)	16/18 (89)
Treatment effect on neurocognitive status	12/15 (80)	11/12 (92)
Neuro-cognitive test that showed effect(s)	**Frequency**	**Only Positive Association (%)**
Bayley Scales of Infant Development III	14/17 (82)	13/14 (93)
Mullen Scales of Early Learning	3/4 (75)	2/3 (67)

Only two articles exhibited a non-exclusively positive association between nutrition and neuro-cognitive measures, and only one article did not exhibit an exclusively positive treatment effect on neuro-cognitive status. One was the study by Mireku et al. (2015) investigated the association between hemoglobin levels during pregnancy and infant cognitive function, which found that infant cognitive scores increased with hemoglobin concentration up to a certain point, after which they started to decline again. This study involved a treatment, and therefore was also the article in which the treatment did not exclusively have a benefit on neuro-cognitive measures of the infant.

The other article that did not exclusively show a positive association between nutrition and neuro-cognitive status was by Markhus et al. (2018), which had mixed findings. While there was an association between lower gross motor skills and mothers taking iodine-containing supplements, this study also found that insufficient iodine intake was associated with lower language skills in infants. The mixed findings found in Mireku et al. (2015) and Markhus et al. (2018) emerged during secondary analyses and thus must be regarded as exploratory findings.

Regarding the specific neuro-cognitive domains displaying relation to nutritional factors, neuro-cognitive effects were found most often in the language, motor, and cognition/executive function/inhibitory control domains (see Table 7).

Table 7

Neuro-cognitive Domain-Specific Effects Observed

Neuro-cognitive effect observed	Frequency	%
Language	14/17	82
Cognition/executive function/inhibitory control	10/17	59
Visual acuity	1/17	6
Motor	10/17	59
Socio-emotional	3/17	18
Composite scale result reported	3/19	16
Effects reported in multiple domains	13/17	67

Summary of Findings

The initial search of the pilot study yielded 657 citations, which were reduced to 177 citations after further evaluation. Among these, 21 articles were selected and scrutinized for review in this pilot systematic review. Of these selected articles, 86% demonstrated a significant correlation between nutrition and neuro-cognitive measures. Of these articles, all but two found an exclusively positive association between nutrition and neuro-cognitive measures.

One standout article, Mireku et al. (2015), investigated maternal prenatal anemia's effect (measured by maternal prenatal hemoglobin levels) on infant neuro-cognition. It revealed that increased maternal hemoglobin levels had a positive impact on infant neuro-cognitive scores up to a certain concentration on the MSEL, above which infant neuro-cognitive levels began to decline.

The other standout article by Markhus et al. (2018) found that the infants of mothers taking an iodine-containing supplement were associated with lower scores on the gross motor skills domain, but no other domains showed this negative association. The study was examining the effects of maternal insufficient iodine status on infant neuro-cognition, and in addition to their finding regarding iodine-containing supplements, they also found that insufficient iodine intake in pregnancy was associated with lower language skills up to 18 months of age. These two standout studies with mixed findings, however, arose out of secondary analyses and must be regarded as exploratory.

Most studies selected for review took place in LMIC settings, used a randomized controlled trial study design, and utilized the BSID III rather than the MSEL. The study found that most studies selected measured biomarkers, but a minority measured micronutrient levels. Furthermore, of the studies which used an intervention not all used a placebo group or measured baseline biomarkers. Just half of the intervention studies which used the MSEL included a placebo group, but all of them measured baseline biomarkers, meanwhile most (83%) articles that used the BSID III included a placebo group and 76% measured baseline biomarkers. Just half of the articles using the MSEL used both placebo group and baseline biomarkers, and just over half (59%) of articles using the BSID III used both placebo group and baseline biomarkers.

The domain in which nutrition-related neuro-cognitive effects were most common for both the MSEL and BSID III was language, followed by motor and cognition/executive control/inhibitory control.

Discussion

Pilot Systematic Review: Proof of Principle

The primary purpose of this thesis was to establish a pilot version of a proposed large-scale systematic review which aims to compare the BSID III and MSEL in the existing literature involving nutrition and neuro-cognitive development, especially in LMIC countries. This pilot study reviewed only a highly sited subset of the relevant articles using the BSID III to measure neuro-cognitive development in the nutritional context. As well, the literature search revealed substantially fewer studies utilizing the MSEL than we expected. That is, the majority of studies used the BSID III to measure neuro-cognitive development in the context of nutrition. The pilot study thus cannot provide a comprehensive analysis of the value of the MSEL and BSID III for use in monitoring infants' nutrition-related neuro-cognitive development. However, the pilot study does indicate that our search and coding strategies were effective in providing at least a small set of relevant articles within which a comparison could be undertaken regarding nutrition-related neuro-cognitive effects. In this sense, the pilot review points to the value of the approach we are adopting as we undertake the proposed large-scale systematic review.

Pilot Review: Preliminary Findings

Regarding possible relationships that emerged in the pilot review between nutritional factors and neuro-cognitive development, a majority of studies in our review found statistically significant associations of nutritional factors with both the BSID III and the MSEL. This was true across several different types of studies (e.g., prospective cohort studies, intervention studies, etc.). Moreover, when nutritional interventions were undertaken – for example, in the context of randomized controlled trials – the majority of studies revealed significant benefits of such interventions on both MSEL and BSID III outcome scores.

While most of the treatments provided a benefit for infants' neuro-cognitive functioning, it is noteworthy that one study found that iodine-containing supplements taken by a mother prenatally were associated with poorer results on neuro-cognitive (i.e., gross motor) outcomes (Markhus et al., 2018), and another by Mireku et al. (2015) found that while infant neuro-cognitive scores increased with maternal hemoglobin levels, there was a certain threshold at which maternal hemoglobin levels raised high enough that neuro-cognitive scores started to decline. However, because these studies were observational and thus assessed correlational relationships, there is not a basis for drawing causal conclusions from either study, and this should be regarded as exploratory findings.

Within the five domains measured by the BSID III and the MSEL, the language domain showed the highest percentage of nutrition-related benefits (82%), followed by cognition more generally (59%), and motor (59%) domains.

Limitations and Future Directions

The articles included in the review were not assessed for bias in the research. One way in which we assessed the scientific quality of articles in this pilot review was through assessing the intervention articles for their use of a placebo group and measuring biomarkers at baseline. The use of placebo groups is important to assess the efficacy of a treatment, so their absence could be a potential indicator of poor research quality. These and other techniques for assessing research quality of each article selected for review would be useful to include in the future large-scale systematic review. Information included in this assessment of quality should consider biases in the results or conclusions (e.g., drawing causal conclusions based on correlational findings), flaws in the study design (e.g., lack of baseline measures, lack of a control, etc.), or questions raised about validity of the findings (e.g., small sample size, small effect size, etc.). Without such an assessment of bias, it is difficult to assess the reliability of the findings, which will be important in ensuring the significance of any conclusions regarding the use of the MSEL and BSID III in nutritional studies. Future reviews of this body of literature should also code for the effect sizes in each selected article, which would help with estimating the likely meaningfulness and replicability of any associations reported in selected articles.

Furthermore, in the proposed large-scale systematic review (for which this thesis was a pilot), it may be beneficial to impose more criteria for exclusion and inclusion on the large set of articles to be narrowed down for selection. Some of these criteria could include a minimum sample size of infants; only including studies involving an intervention, or even more specifically a micronutrient supplementation as an intervention; and the use of more than one neuro-cognitive instrument to assess neuro-cognition in the participants.

Conclusion

This pilot systematic review has established a foundation for a proposed large-scale systematic review aimed at comparing the value of the MSEL and BSID III for use in monitoring infants' neuro-cognitive development in nutritional studies in LMIC settings. The devised search strategies, including search terms and inclusion and exclusion criteria, have provided valuable insights into the landscape of articles that use the MSEL or BSID III in nutritional research. The process of coding and analyzing the chosen articles in this pilot review allowed us to develop a coding system to identify specific dimensions of method and results that will be informative regarding the MSEL versus BSID IIII comparisons of interest. Additionally, the pilot review helped to highlight the need for additional sources of information, such as effect sizes, when the proposed large-scale systematic review is undertaken.

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