Nutrition, growth and neurodevelopment in children from low resource settings in India

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ABBREVIATIONS

BSID-III	Bayley Scales of Infant and Toddler Development, 3rd Edition
CBCL	Child Behavior Checklist- preschool
CHRD-SAS	Centre for Health Research and Development, Society for Applied Studies
ciKMC	Community-initiated Kangaroo Mother Care
CI	Confidence interval
CVS	Crichton Vocabulary Scales
DHS	Demographic and Health Surveys
ECD	Early child development
ECDI	Early Childhood Development Index
ERB	Ethics Review Board
GAM	Generalized additive model
GEE	Generalized estimating equation
GLM	Generalized linear model
HAZ	Height for age z-score
HOME	Home Observation for Measurement of the Environment
ICC	Intraclass correlation
IFA	Iron-folic acid
IGF-1	Insulin-like growth factor-1
ITS	Infant Temperament Scale
IQ	Intelligence quotient
KMC	Kangaroo Mother Care
LAZ	Length-for-age z-score
LBW	Low birth weight
LMICs	Low-middle-income countries
MD	Mean difference
MICS	Multiple Indicator Cluster Survey
MMN	Multiple micronutrients
NEPSY-II	Neuropsychological test battery, 2nd edition

OR	Odds ratio
PER	Protein energy ratio
PROCESS	Pediatric Review of Children's Environmental Support and Stimulation
RCT	Randomized controlled trial
RDA	Recommended daily allowance
SD	Standard deviation
SDGs	Sustainable Development Goals
SE	Standard error
SQ-LNS	Small quantity lipid-based nutritional supplement
WHO	World Health Organization
WHZ	Weight-for-height z-score
WISC-IV^{INDIA}	Wechsler Intelligence Scale for Children 4th edition (India)

SCIENTIFIC ENVIRONMENT

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SUMMARY (ENGLISH)

Background: Children in low-middle-income countries (LMICs) often do not reach their full developmental potential due to unaddressed factors such as suboptimal nutrition and insufficient early child stimulation.

Objectives: To identify the contribution of linear growth, nutritional supplementation, and early child stimulation, in combination or alone, on neurodevelopment. More specifically (i) to determine the impact of cereal mixes with varying amounts of dairy protein and multiple micronutrients (MMNs) on neurodevelopmental scores at 12 and 24 months of age (ii) to examine the association between changes in linear growth during the period from 24 months to 6-9 years of age and cognitive functions at 6-9 years (iii) to ascertain whether enhanced early child stimulation could safeguard low birth weight (LBW) infants with growth deficits against developing poor neurodevelopmental scores.

Methods: The three studies utilized RCT data, with one using RCT-design and the others, a cohort approach. Multiple regression models were used to obtain effect estimates.

Results: Infants who received cereal mix with a moderate amount of dairy protein showed improved motor and temperament scores compared to the control group, but only at 12 months of age. Higher dairy protein intake was associated with lower socio-emotional scores and a more difficult temperament, compared to modest protein intake. Length-for-age z-score (LAZ) between 12-36 months was positively associated with cognitive and executive function at 6-9 years. No significant association found between the changes in LAZ from 12-36 months to 6-9 years and cognitive or executive function at 6-9 years. LBW infants with sub-optimal stimulation had a stronger association between LAZ and neurodevelopmental scores than those with adequate stimulation.

Conclusions: High quality protein and MMNs during infancy is unlikely to have a sustained impact on neurodevelopment. Neurodevelopment in middle childhood may not be associated with changes in linear growth after two years of age. Nurturing care is particularly important for LBW babies with poor growth.

Consequences: To ensure a sustained impact on neurodevelopment, the focus should be on improving linear growth and the quality of early child stimulation in the first 24 months.

SAMMENDRAG (NORWEGIAN)

Bakgrunn: Barn fra lav-middelinntektsland når ofte ikke sitt utviklingspotensial på grunn av dårlig ernæring og dårlig tilrettelegging for læring og utvikling.

Målsetninger: Å beskrive sammenhengen mellom lineær vekst, ernæringstilskudd og tilrettelegging for læring og utvikling alene og barns kognitive utvikling. Spesifikke målsetninger; (i) å måle effekten av tilskudd med kornbasert mat med forskjellige mengder melkeprotein og mikronæringsstoffer på kognitiv utvikling ved 12 og 24 måneders alder, (ii) å undersøke sammenhengen mellom endring i lineær vekst utover 24 måneders alder med kognitiv utvikling senere i barndommen, (iii) å undersøke om optimal stimulering er assosiert med kognitiv utvikling hos spedbarn født med lav fødselsvekt og som vokser dårlig etter fødsel.

Metoder: Alle tre studiene brukte data fra kliniske studier (RCT), hvor den ene brukte RCT-designet og de to andre en kohorttilnærming. Multippel regresjon ble brukt for å analysere data.

Resultater: Spedbarn som fikk kornblanding med en moderat mengde meieriprotein hadde noe bedre skårer på motorikk og temperament sammenlignet med spedbarn i kontrollgruppen. Denne effekten ble kun sett ved 12 måneders alder. Et høyt melkeproteininntak var assosiert med lavere sosio-emosjonelle skårer og et vanskeligere temperament. Det var en sammenheng mellom lengdevekst de første 24 månedene, men ikke utover 24 måneders alder, og kognisjon ved 6-9 års alder. Hos spedbarn som fikk lite utviklingsstøtte, var assosiasjonen mellom vekst og utviklingsskårer sterkere enn hos de som fikk mere støtte.

Konklusjoner: Kosttilskudd med melkeprotein og mikronæringsstoffer i en kort periode i spedbarnsalderen, bedrer ikke kognitiv utvikling hos Indiske spedbarn. Lineær vekst etter de to første leveårene var ikke assosiert med barnets utvikling. Kvaliteten på stimulering og omsorg var spesielt viktig for barn født med lav fødselsvekt og med dårlig vekst.

Konsekvenser: Innsats for å forbedre lineær vekst og forbedring av kvaliteten på stimulering hjemme bør gjennomføres de første 24 månedene av livet.

LIST OF ARTICLES

Paper- I

Upadhyay RP, Taneja S, Strand TA, Hysing M, Koshy B, Bhandari N, Bahl R. Milk-cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomized controlled trial in India. Br J Nutr. 2022:1-26. doi: 10.1017/S0007114522003944.

Paper-II

Upadhyay RP, Hysing M, Taneja S, Kvestad I, Bhandari N, Strand TA. Linear Growth between Early and Late Childhood and Cognitive Outcomes at 6-9 Years of Age. J Pediatr. 2020;225:214-221.e3. doi: 10.1016/j.jpeds.2020.05.043.

Paper-III

Upadhyay RP, Taneja S, Strand TA, Sommerfelt H, Hysing M, Mazumder S, Bhandari N, Martines J, Dua T, Kariger P, Bahl R. Early child stimulation, linear growth and neurodevelopment in low-birth-weight infants. BMC Pediatr. 2022;22(1):586. doi: 10.1186/s12887-022-03579-6.

Contribution:

Paper I: Proposal writing and securing grant; supervising the implementation; preparing the plan of analysis; conducting statistical analysis and manuscript writing.

Paper II: conceptualization of the scientific question; preparing the plan of analysis; conducting statistical analysis and manuscript writing.

Paper III: conceptualization of the scientific question; preparing the plan of analysis; conducting statistical analysis and manuscript writing.

INTRODUCTION

With improvement in medical and obstetric care, the rates of neonatal, infant and under-five mortality in low-middle-income countries (LMICs) have come down significantly (1). Consequently, the issue of whether the children in these settings are thriving appropriately and to the best of their capabilities is an issue that has gained focus and momentum in the recent years. A substantial proportion of under-five children in LMICs live in poverty and are at risk of not being able to fulfil their potential for physical growth and cognitive development (2,3). It is, therefore, crucial that children living in these resource constrained settings are assessed for their optimal growth and development and interventions are designed to address the modifiable risk factors for poor growth and development.

The following sections present contemporary data on the burden of linear growth faltering and sub-optimal early child development (ECD), with particular focus on the risk factors for poor ECD and known interventions for improving child development. Towards the end of this section, key evidence gaps have been presented that form the basis for the research questions dealt with in this thesis.

Burden of linear growth faltering and sub-optimal early child development in low-middle-income settings

Linear growth

Children in LMIC settings are known to be at -risk of linear growth faltering (4,5). According to the recent estimates, around 27% of the total under-five children in LMICs were stunted (length/height for age z-score, LAZ/HAZ <-2 SD) in the year 2017 (3). Although there has been a decline in these estimates (i.e., from around 37% in 2000), the burden is still substantial. Globally, there is a skewed distribution with nearly 85% of the stunted children concentrated in Asia and Africa (3). India (29%), Pakistan (7%), Nigeria (6.5%) and China (9.0%) contribute to around 50% of the stunted children globally (3). Using published estimates as well as individual-level data from population-based surveys, a recent study from 137 developing countries estimated the most important risk

factors for stunting in children (6). Intrauterine foetal growth retardation, specifically, term small for gestational age and prematurity contributed to nearly 33% of stunting in children aged 2 years (6). This was followed by environmental factors such as poor sanitation, unimproved water and use of biomass fuel that contributed to around 22% of the stunting (6). Maternal nutrition and infection related factors (contributing to around 14% of stunting) and children nutrition and infections (contributing to 13.5% of stunting) were other important risk factors (6).

Early child development

It is documented that over 200 million children (nearly 43% of all children) in LMICs are unable to reach their full developmental potential (2,7). Using data from the Multiple Indicator Cluster Survey (MICS) and the Demographic and Health Surveys (DHS) programs in 35 LMICs (including 99,222 children aged 3-4 years), McCoy et al documented that around 81 million children aged 3 and 4 years had low cognitive and/or socioemotional development scores (8). Around 15% of children had low scores in the cognitive domain, 26.0% had low socioemotional scores, and 37% performed poorly in either or both domains. The largest number of affected children were in sub-Saharan Africa (~44% of children), followed by South Asia (~38%) and the East Asia and Pacific region (~26%) (8).

Importance of early child development and risk factors for poor development

ECD is viewed as a multi-faceted holistic concept that refers to physical, motor, cognitive, linguistic and social-emotional functioning in young children (9). The promotion of ECD has the potential to transcend and influence all major goals and targets of Sustainable Development Goals (SDGs). However, it more closely relates to Goal 4, Target 4.2 which states that by 2030, countries should 'ensure that all girls and boys have access to quality early childhood development, care and pre-primary education so that they are ready for primary education' (10). The early years of life, preferably the first five years, lay the groundwork for lifelong development, and skills developed prior to school entry help determine children's academic success (11). It is important to assess children during this vulnerable period to determine if they are

developing appropriately, and if not, to identify and design intervention to address the potential risk factors.

Poor development in children is multi-factorial. Table 1 below summarizes the important risk factors on which there is sufficient evidence available (12,13). The table draws inspiration from the Lancet series on Early Child Development in Developing Countries (12,13). The important risk factors include malnutrition resulting in poor linear growth (reflected as stunted growth), micronutrient deficiencies (such as iodine deficiency, iron deficiency anaemia), adverse birth outcomes (such as low birth weight, prematurity and intra-uterine growth retardation), lack of childhood stimulation and learning opportunities, infections and environment toxins. Poverty is a major element that accompanies most of these risk factors (7,13,14). It is quite common for children growing in socio-economically deprived setting to be exposed to multiple risk factors that together affect development adversely.

Table 1. Risk factors for child development with sufficient available evidence

Risk factor(s)	**Evidence**
Inadequate child stimulation	Children exposed to environments with lack of optimal care, stimulation and opportunities for learning are at risk of poor intelligence quotient (IQ) and behavioural outcomes (15-17). Recent data from Nepal showed lower cognitive and language scores in infants with parents reporting of physically punishing the child and not engaging in spontaneous vocalization (18)
Linear growth deficit	Meta-analysis from LMICs using publicly available data from fifteen Multiple Indicator Cluster Surveys (MICS-4) shows stunted children to have poorer neurodevelopmental and learning outcomes (19). Severe stunting (HAZ <-3) was negatively associated with overall development. Severe and any stunting (HAZ <-2) was negatively associated with literacy/numeracy development. Any stunting was negatively associated with learning. No clear association was observed between stunting and socio-emotional development.
Iodine deficiency	Children deficient in iodine have been shown to have lower development than iodine replete

	children. Iodine deficiency during pregnancy causes congenital hyperthyroidism and poor development in childhood (20). Around 7 to 11 IQ points lower in iodine deficient children compared with iodine replete children (21).
Iron deficiency anaemia	Iron deficiency anaemia associated with developmental deficits, both short and long term. Compared with those without anaemia, children with anaemia likely to have neurodevelopmental disorders (OR 2.1) and learning disability (OR 2.2) (22). A previous meta-analysis documented that with each 1.0 g/dL decrease in haemoglobin concentration, there is an associated decrease of around 2 IQ points (23)
Malaria	Severe malaria, particularly cerebral malaria, has been linked to persistent neurological, behavioural, and cognitive impairments (24-26). Deficits in attention, memory, visuo-spatial skills, language, and executive functions may occur after malaria infection (26). Severe malaria (cerebral malaria) has been shown to be associated with persisting impairments in up to 24% of childhood survivors (27).
Maternal depression	Maternal perinatal depression and anxiety is associated with poorer offspring social-emotional, cognitive, language, motor development and adaptive behaviour (28-30). The mean cognitive score for children with mothers having post-partum depressive symptoms were around 0.25 standard deviation (SD) lower in a meta-analysis conducted using 14 studies (31)
Low birth weight including prematurity and intra-uterine growth retardation	Evidence from a meta-analysis indicates that children born low birth weight (<2500 grams at birth) have lower cognitive (0.30 SD) and motor scores (0.27 SD) compared to children with normal birth weight (32). Children born preterm have, on average, around 0.80 SD lower IQ scores compared to those born at term, based on findings from a meta-analysis (33).
Exposure to environmental toxins	Meta-analysis and systematic reviews suggest negative association between heavy metal exposure (lead, arsenic, mercury, cadmium, and manganese) and neurodevelopment (34,35).
Child violence and abuse	Findings from prospective longitudinal studies showed physical punishment to consistently predict increase in child behaviour problems (36)

Poor linear growth as a risk factor for sub-optimal child development

Children with poor linear growth are at risk of suboptimal cognitive, psychological, language, and motor performance as well as poor academic performance (19, 37). Children who are stunted by 24 months are estimated to typically earn 10–20 percent lower wages throughout their productive lives, compared to their healthy non-stunted counterparts (7). According to previous estimates released by the World Bank, 1% loss in adult height due to stunting during childhood is associated with 1.4% loss in economic productivity (38). A meta-analysis of data from nearly 58,000 children aged 36 to 59 months from 15 low middle income countries explored the association of stunting with the Early Childhood Development Index (ECDI) scores reflecting physical, learning, literacy/numeracy and socio-emotional development (19). It was observed that both severe stunting (HAZ <-3) and any stunting (HAZ<-2) were negatively associated with overall on-track development (defined as "on track in three or four domains") and literacy/numeracy development (OR=0.45). Any stunting was negatively associated with learning (OR=0.79). However, no clear association between stunting and socio-emotional development could be established (19). On similar lines, optimal linear growth has been shown to be associated with better developmental outcomes. A meta-analysis of 68 studies from 29 LMICs showed that each unit increase in HAZ for children ≤2 years was associated with a 0.22-SD increase in cognition at 5 to 11 years (39).

Inadequate stimulation and learning opportunities as a risk factor for sub-optimal child development

Children exposed to environments with lack of optimal stimulation, responsive care and opportunities for learning are considered to be at risk of poor cognitive and developmental outcomes and *vice-versa* (13,40). Data from observational studies have supported this. A recent analysis of data from 600 Nepalese infants showed that parental reports of physical punishment and lack of spontaneous vocalization was associated with poor cognitive and language scores (18). Children with caregivers that did not attempt spontaneous vocalization with the child had around 4 points lower language scores than those who had caregivers that showed such stimulation (18). Also, children that were

reportedly exposed to parental punishment had around 2 points lower cognitive scores compared to those who were not (18). Another study from rural India among 516 low-birth-weight infants documented improved child stimulation at home to be positively and significantly associated with cognitive, motor and language scores (41).

Available data indicates lack of optimal stimulation and childcare practices in families from low-middle-income settings. A recent analysis of survey data from the Multiple Indicators Cluster Survey (MICS) and the Demographic and Health Survey (DHS), representing 62 low-middle-income settings found that the proportion of children exposed to quality stimulation by parents were quite low (42). Around 40% of the mothers and 12% of the fathers provided high quality stimulation, defined as engagement in a minimum of 4 out of 6 activities with the child (42). The activities included reading books or looking at picture books; telling stories; singing songs or lullabies; taking the child outside the home; playing with the child; and naming, counting, or drawing things for or with the child. The study also found that poorest households had, lower levels of stimulation, compared to economically well to do households (42).

Nutritional and child stimulation interventions to improve early child development

Table 2 provides evidence for interventions addressing the well -established risk factors for poor early child development. For the purpose of the thesis, we intended to focus on nutritional risk factors and factors related to child stimulation and learning opportunities. There were two main reasons for doing so:

1. Inadequate nutrition and child stimulation are common modifiable risk factors for sub-optimal ECD in children from LMICs.
2. The primary trial and the datasets (for secondary data analysis) available at the time of planning of thesis were related to nutrition, linear growth and had a significant component of child stimulation.

Table 2. Effect of interventions to address known risk factors on child development

Risk factor(s)	Evidence on effect of intervention
Inadequate child stimulation	Evidence from intervention studies note both concurrent and long-term beneficial effect of child play and learning opportunities on neurodevelopment. Benefits from interventions to provide stimulation or learning opportunities range from 0.30 to 0.70 SD increase in cognitive, language, motor and socio-behavioural scores (43-45)
Linear growth deficit	Nutritional interventions (both macro and micro-nutrients) to children have been shown to improve HAZ (0.07 SD), reduce proportion of children with stunting, wasting and underweight (around 12-14% reduction) and concurrently lead to improvement in cognitive (0.08 SD), language (0.13 SD), motor (0.08 SD) and socio-emotional (0.08 SD) scores (46-48)
Iodine deficiency	Meta-analysis on iodine supplementation to mother (mild to moderately deficient) during pregnancy suggests no effect on child cognitive, behavioural or language scores; some improvement in motor scores was found (49,50)
Iron deficiency anaemia	Effects on child development uncertain; meta-analysis on the effect of daily iron supplementation on health in children aged 4-23 months identified no evidence of effect on mental or psychomotor development (51) Another meta-analysis among children and adolescents (5-19 years of age) found iron supplementation to positively impact intelligence test scores only but not attention, short-term memory, long-term memory, or school performance (52)
Malaria	A study in Tanzania utilizing data from the Malaria Atlas Project and the Uwezo household surveys found that a ten percentage-point decrease in malaria prevalence was associated with a 0.06 SD increase in English literacy achievement among children (53) Meta-analysis on the effect of anti-malarial treatment found an effect on cognitive function in children older than 10 years (0.36 SD) (54)
Maternal depression	Meta-analysis of published literature from LMICs did not note interventions aimed at promotion of maternal mental health to benefit child cognitive and psychomotor outcomes (55) Evidence from another systematic review suggests that intensive and sustained interventions aimed at

	management of maternal postnatal depression might improve cognitive development (56)
Child violence and abuse	Meta-analysis of randomized controlled trials suggests benefits of positive parenting interventions on child cognitive development (0.32 SD), language development (0.28 SD), motor development (0.24 SD), socioemotional development (0.19 SD) and reductions in behaviour problems (43)

Nutritional interventions and early child development

A meta-analysis, using data from 48 studies involving 29,814 children from 20 developing countries, reviewed the impact of nutritional supplementation on cognitive development of children (57). The review found that childhood nutritional supplementation improved cognitive development (0.08 SD; 95% CI 0.03 to 0.13) and those with ≥5 nutrients was particularly beneficial (0.15 SD; 95% CI, 0.08 to 0.22) (57). The authors noted that supplementation within the age group of 6-18 months (0.09 SD; 95% CI, 0.02 to 0.15) and for a duration of at least 6 months (0.08 SD; 95% CI, 0.02 to 0.13) led to significant improvements in cognitive score (57). The meta-analysis also found that standalone supplementation with iron, calcium, zinc, Vitamin B2 and protein had a statistically significant impact on cognitive scores in children (57). Another review by Prado et al showed that the combined macro and micro-nutrient supplementation among children improved their growth (LAZ 0.07 SD), cognitive (0.08 SD), language (0.13 SD), motor (0.09 SD) and socio-emotional (0.09 SD) scores (46). An individual participant data meta-analysis comprising of data from 14 randomized controlled trials with more than 37,000 children aged 6 to 24 months showed that supplementation with small-quantity lipid-based supplement along with multiple micronutrients improved language (0.07 SD), motor (0.08 SD) and socio-emotional (0.08 SD) scores as well as led to a 12-14% reduction in stunting, wasting and underweight at 24 months of age (47,48).

Interventions for stimulation and learning opportunities and early child development

A large cluster randomized trial from Pakistan found that responsive stimulation interventions, when delivered through community health workers, could significantly improve neurodevelopment outcomes (in the range of 0.5 to 0.7 SD) in children aged 24 months (45). However, when these children were followed up and assessed again at 4 years of age, the positive effect of the responsive stimulation interventions persisted but the effect sizes were modestly reduced (0.1 SD for IQ, 0.3 SD for executive functioning, 0.2 SD for pre-academic skills and 0.2 SD for pro-social behaviours) (58). Nonetheless, the findings suggest that child stimulation and learning opportunities when provided very early in life could have persisting effects. Another cluster randomized trial in underweight Bangladeshi children aged 5-24 months aimed at integrating an early childhood development programme into primary health care and understand the effects on various domains of development (59). The study found substantially improved effects on children's cognition (1.3 SD), language (1.1 SD) and motor score (1.2 SD). Meta-analysis of studies with interventions aimed at promotion of responsive care and provision of learning opportunities in young children have documented significantly higher cognitive, language, motor and social-emotional development scores, compared to those that did not receive adequate responsive care and learning opportunities (43,44,60).

Evidence gaps

Our understanding of the factors that influence early child development is incomplete, particularly in terms of how these factors interact with each other. This thesis focuses on addressing some of the evidence gaps related to nutrition and child stimulation in resource-constrained settings. By doing so, we hope to gain a better understanding of how these factors impact early childhood development and how they can be effectively addressed.

Lack of clarity on the relationship between linear growth and child development

The relationship between linear growth in the first two years of life and concurrent as well as later development in children is well documented (39,61,62). Children who are

stunted or those with linear growth deficits have been shown to have suboptimal cognitive, psychological, language, and motor performance as well as poorer academic performance (19,37). It is believed that in the early formative years of life, both poor linear growth and sub-optimal neurodevelopment share overlapping causes such as inadequate nutrition, high burden of infections and hospitalization, and sub-optimal care at home (63,64). The presence of any of these exposures, either alone or in combination may therefore negatively impact both growth and development.

It is thought that it is difficult to reverse the growth deficits beyond the first 2 years of life primarily because the children continue to remain living in the deprived environments that contributes to poor growth (63,65,66). However, contemporary studies have shown that recovery from growth failure can occur (67-70). This further demands an exploration of whether this recovery could also improve their cognitive and behavioural functioning. Prado et al in their recent meta-analysis showed that nutritional supplementation studies in older children had comparatively higher impacts on linear growth compared to child development outcomes (46). Further, studies that focused on child stimulation had higher impact on development outcomes compared to growth (46). These findings together indicate that the factors that influence linear growth and cognition in later childhood may either not be entirely similar and therefore, an analytic approach to understand the dynamic relationship between linear growth and child neurodevelopment during the early childhood is essential.

Do linear growth and child stimulation interact to influence each other's individual association with early child development?

Both linear growth and child responsive care and stimulation are known to be associated with neurodevelopment in children (18,39,41,43-45). However, evidence is limited on how these two exposures, when present together, influence each other's association with neurodevelopment. Black *et al*., using a sample of 513 infants from rural India, showed that a nurturant home environment attenuated associations between linear growth and fine motor and receptive language development (71). A multicentre study from Burkina Faso, Ghana and Malawi did not detect significant association between linear growth

faltering and child development in the context of a high-quality developmental stimulation (62). A study from rural Vietnam noted a modest beneficial effect of early child development interventions on cognition among children with declining height-for-age Z-scores or those that were stunted (72). These findings indicate that in the presence of an environment characterized by nurturance and learning opportunities, children with low LAZ can acquire developmental skills at the same level as their peers. Contrasting these findings, recent studies from Malaysian and Jamaican infants found no significant influence of quality of child stimulation at home on the association between LAZ status and cognitive outcomes (73,74). Reliable evidence is therefore required on whether in a setting with socio-economic constraints, a moderate to high-quality home environment can protect children with growth deficits from attaining poor development scores.

How does supplementation with specific nutrients (protein and multiple micronutrients) impact child neurodevelopment outcomes

Complementary feeding is usually inadequate in resource-poor populations in LMICs (75). The concerns are with the quantity and quality of complementary foods, as the infants often fail to achieve the intake of key nutrients required to achieve optimal growth and neurodevelopment (75,76). In addition to the total energy the infant gets from breast milk and complementary foods, there are important unanswered questions about the importance of the quality of complementary foods. Of particular importance is the protein and micronutrient content of the diets. Most of the micronutrients play a major functional role in the central nervous system and stimulate nerve cell differentiation, migration and differentiation (77-79). Micronutrients such as iodine, iron and vitamin B12 have been documented to play an important role in brain development (77-79). Proteins are specially required in neurogenesis, neuronal migration, and differentiation, synaptogenesis, oligodendrocyte myelination, neurotransmitter production and reuptake, and maintaining electrical efficiency (79-81). Proteins, especially those obtained from dairy, have been documented to increase insulin-like growth factor-1 (IGF-1), a neurotrophic polypeptide with crucial role in growth, development and maturation of the central nervous system (82-84).

Analysis of complementary foods for 6–12-month-old infants in poor populations in India showed that adequate intake of important nutrients could not be achieved using home available foods (85,86). Around 10-15% of total daily protein intake for growing infants and young children from animal source is considered to be optimal (87). Home based complementary feeds in low resource settings have lower utilizable proteins and are low or lacking in necessary amino acids and micronutrients (88). The efficiency of utilization of dietary protein depends upon its digestibility and absorption of the released amino acids. Plant based proteins, mainly in cereals, legumes and vegetables, are of poorer quality than animal proteins, not only because of their lower digestibility but also because they are limited in one or more of the essential amino acids (89). A review on the quality of complementary foods in poor resource settings documented that around 50-75% of the total protein a child eats is from cereals and other plant sources (88). Studies have suggested that protein quality is relatively poor in diets that derive over 50% of protein from cereal sources, thereby limiting protein utilization, which in turn may adversely impact overall growth and development (88,90). It is plausible that higher daily protein intake may achieve larger effects on neurodevelopment and this hypothesis needs testing.

Evaluation of a supplementation strategy to achieve an adequate intake of high-quality protein and micronutrients may be particularly interesting to evaluate in resource-poor settings, where infants often have high infection load as well as poor gut health characterized by gut inflammation and immune activation (91,92). In such situations, requirements of high-quality proteins, micronutrients and other specific nutrients may be enhanced. In India, food insecurity is addressed through public food distribution systems, ready-to-cook mixes of raw foods and supplementary nutrition through the Anganwadi centres (93). The design of what is offered largely attempts to fill the calories gap. The questions about protein content- how much and its quality, and specific nutrients remain unanswered. Without new evidence on importance of protein and other specific nutrients in young infant complementary feeding, change in policy is difficult. Proving reliable scientific evidence in this aspect will help governments and implementing agencies design better nutrition programmes for infants.

AIMS AND OBJECTIVES

The aim was to identify the role of different exposures, particularly nutritional supplementation, linear growth and stimulation, in combination or alone, during infancy and/or early childhood on neurodevelopmental outcomes.

The specific objectives of this thesis were:

1. To test the efficacy of supplementing two milk cereal mixes enriched with multiple micronutrients and with varying amount of protein (modest and high amounts of protein) during 6-12 months of age, compared to no supplementation, for their effect on neurodevelopment scores at 12 and 24 months of age.
2. To examine whether improvements in linear growth between early and late childhood can lead to improved cognitive and higher executive functions at ages 6 to 9 years
3. To assess whether, in a setting with socio-economic constraints, optimal stimulation and nurturance at home could protect LBW infants with growth deficits from attaining poor neurodevelopment scores.

METHODS

The three studies addressed different research questions, though all converge on a common theme of early child development. The first study was a RCT done with the aim to test the effect of micronutrient enriched milk-cereal based supplements, differing in their protein content, during infancy on neurodevelopmental outcomes (94). The second study examined the association between improvement in linear growth beyond 2-3 years of age and child cognition and higher executive functions at ages 6-9 years (95). The third study examined whether linear growth and child stimulation at home, among low-birth-weight infants, influence each other's association with cognitive, motor and language scores during end of infancy (96). The two latter studies i.e., study 2 and 3, were analysed in a cohort design.

Table 3. Summary of the key methodological features for the three studies

	Study 1	**Study 2**	**Study 3**
Objective	To measure the effect of two milk-cereal mixes with modest and high amounts of protein and enriched with multiple micronutrients, given between 6-12 months, on neurodevelopment at 12 and 24 months of age, compared to no-supplementation.	To understand whether improvements in linear growth and/or change in stunting status between early and late childhood can lead to improved cognitive outcomes at ages 6 to 9 years	To measure the extent to which linear growth and early child stimulation modify each other's association with neurodevelopmental outcomes among LBW infants.
Study design	RCT (unblinded)	Secondary analysis of data from follow-up study of children enrolled in an RCT	Secondary data analysis using data from an RCT
Sample size	N=1134 at 12 months N=1214 at 24 months	N=791	N=516
Study site	Urban Delhi, India	Urban Delhi, India	Rural and semi-urban Haryana, India
Study population	Infants aged 6 months at time of enrolment	Children aged 6 to 9 years	LBW infants
Exposure(s)	Milk-cereal mixes with varying amounts of protein,	Change in HAZ between early (12-36 months) and late	LAZ at 6 months of age and child stimulation at 12

	supplemented daily for a period of 180 days, starting from 6 months of age	(6-9 years) childhood	months of age
Outcome (s)	Cognitive, motor, language and socio-emotional scores at 12 and 24 months of age Infant temperament at 12 months Behavioural problems at 24 months	General intellectual ability and verbal skills Executive functioning	Cognitive, motor, language and socio-emotional scores at 12 months of corrected age
Ethics Review Board (ERB) approvals	Ethics committee of the Centre for Health Research and Development, Society for Applied Studies, India (CHRD-SAS) (SAS/ERC/IMPRINT-FU/2019) and Regional committees for medical and health research ethics (REK), Norway (REK 2019/554) The study registered on Clinical Trials Registry-India (CTRI/2019/03/018238)	The parent trial (SAS/ERC-SFAV/Sept09; 2008/3545/OYSV) and the follow up study (SAS/ERC/VitB12/2016; REK 2014/1359) had approvals from ethics committee of CHRD-SAS and REK, Norway Primary (CTRI/2010/091/001090) and the follow up study (CTRI/2016/11/007494) registered at Clinical Trials Registry-India (CTRI)	Primary trial registered at clinicaltrials.gov (NCT02631343); approvals obtained from ethics committee of CHRD-SAS (SAS/ERC/105/2015; WHO ethics review committee (ERC.0002629); REK, Norway (2015/1486/REK vest)
Publications from the same study (PubMed ID)	PMID: 34637505	PMID: 23902779 PMID: 32019814	PMID: 32247311 PMID: 33979366

Study 1: **Milk-Cereal Mix Supplementation during Infancy and Impact on Neurodevelopmental Outcomes at 12 and 24 Months of Age: A Randomized Controlled Trial in India**

Study design, site and study subjects

The study is a part of a parent trial that assessed the impact of nutritional supplementation during infancy on linear growth and biochemical outcomes at 12 months of age (97). The study was conducted in low-resource settings in Urban Delhi, India among 1548 infants. The parent trial was an individually randomized controlled efficacy trial and the participants were enrolled at 6 months of age (+ up to 29 days). A door-to-door survey was conducted by the survey team to identify eligible infants. For inclusion, the infants had to be on continued breastfeeding, with no documented illness requiring prolonged institutional management, not severely malnourished (weight-for-height, WHZ <-3), with no congenital malformations and the family was unlikely to relocate from the study area over the next 6 months (97).

Randomization, allocation, and blinding

Eligible infants were randomized to either one of the two intervention groups (modest-protein or high-protein) or the control group, with an allocation ratio of 1:1:1, through a computer-generated system. The randomization list was prepared using blocks of variable (3 or 6) length. Only one infant was enrolled from each household. It was not possible to blind the study participants and the study teams to the group allocation (i.e., no supplement vs. two supplement groups). However, the milk-cereal mix packets were labelled with 13 letters each to maintain team blinding between the modest- and high-protein groups. The list of letters was provided to the company who manufactured these mixes by the statistician from World Health Organization (WHO), Geneva.

Intervention and co-interventions

Infants in the two intervention groups (modest-protein and high-protein) received packets of milk cereal mix – one packet (25 g) to be consumed daily for a period of 180

days. Infants in the control group did not receive any supplement. Table 4 summarizes the specific details of the interventions and the co-interventions.

Table 4. Interventions and co-interventions in the trial

	Control	Modest protein supplementation group	High protein supplementation group
Intervention(s)			
Daily provision of milk-cereal providing ~125 Kcal, 2.5 g protein (PER of 8%), 30% of protein from dairy source (0.75 g) and micronutrients at 80-100% RDA	No	Yes	No
Daily provision of milk-cereal providing ~125 Kcal, 5.6 g protein (PER of 18%), 30% of protein from dairy source (1.68 g) and micronutrients at 80-100% RDA	No	No	Yes
Co-intervention(s)			
Counselling on continued breastfeeding; immunization; optimal complementary feeding practices; signs of infant illness	Yes	Yes	Yes
Facilitate health care for infant illness	Yes	Yes	Yes
Provision of iron folic acid (10 mg elemental iron and 100 mcg folic acid)	Yes	Yes	Yes
Counselling on appropriate hygiene behaviours	Yes	Yes	Yes

PER- Protein energy ratio; RDA- recommended daily allowance; micronutrients included vitamins A, D, C, E, B12, B6, B1, B2, B3, B5, B7, zinc, calcium, selenium, iodine, magnesium, copper, manganese.

The supplement delivery team visited households of children in the intervention groups weekly to provide milk-cereal sachets. They gathered information on compliance by collecting empty packets and reinforced their intake. Mothers of infants in all the three study groups were counselled by nutritionists on the importance of continuing breastfeeding and on appropriate complementary feeding practices using home foods. Mothers were also taught early recognition of illness, counselled on early care-seeking

and on the importance of childhood vaccines. Iron-folic acid (IFA) drops (1 ml daily that provided 10 mg of elemental iron and 100 μg folic acid) were given to all infants, irrespective of their group allocation.

Outcome assessment

Infants enrolled in this trial were separately consented at 12 months for their neurodevelopmental assessments at 12 and 24 months and anthropometric assessments at 15, 18 and 24 months of age. The primary outcomes were cognitive, motor and language scores at 12 and 24 months of age. The secondary outcomes were socio-emotional scores at 12 and 24 months of age, infant temperament scores at 12 months of age and mean internalizing and externalizing behaviour scores at 24 months of age.

The cognitive, motor, language and socio-emotional scores were assessed using Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) (98,99). Infant temperament was assessed using the Infant Temperament Scale (ITS) and child behaviour was assessed using the Child Behavior Checklist- preschool (CBCL) (100,101). Assessment of environment at home and child stimulation by caregivers was done using the Pediatric Review of Children's Environmental Support and Stimulation (PROCESS) questionnaire at 12 months of age and through the Home Observation for Measurement of the Environment (HOME) tool at 24 months of age (102-104). An independent team of trained and standardized psychologists conducted all the assessments in the study clinic, except for the HOME tool administration which was conducted by trained outcome assessment team members through home visitation. The assessment team was blinded with regard to the intervention groups.

Sample size

The number of children that could be included in this study was driven by the sample size in the parent trial (n=1548). The primary analysis was aimed at testing the effect of milk-cereal based supplements, differing in their protein content, on neurodevelopmental outcomes, when compared to no-supplementation. For this, we considered a 0.25 standard deviation (SD) mean difference in cognitive, motor and language scores at 12

months between the modest-protein group and the no supplement group and a 0.30 SD difference between the high-protein group and the no supplement group. With 90% power, 2-sided 5% alpha level and 20% attrition, 400 infants and 280 infants per group were required for the comparisons between the modest-protein and high-protein groups with the no supplement group respectively. We, therefore, aimed to include a total of around 1200 infants for assessment of neurodevelopment outcomes.

An additional analysis was planned to compare the two supplements with each other for their effect on neurodevelopmental outcomes. With a sample size of 400 infants each in modest-protein and high-protein groups and one-sided alpha level of 5%, we were powered at 80% to detect a difference of around 0.17 SD in cognitive, motor and language scores between the two supplement groups. Overall, 1200 infants were followed up for their neurodevelopment assessments at 12 and 24 months of age.

Study 2: Linear growth between early and late childhood and cognitive outcomes at 6 to 9 years of age

Study design and site

This was a secondary data analysis that utilized follow up data of children that had previously participated in a randomized double-blind placebo-controlled trial on the effect of vitamin B12 and/or folic acid supplementation on childhood infections and growth in New Delhi, India (105,106).

Study subjects, interventions and outcome assessment in the parent trial

Children were recruited at age 6 to 30 months from low- to middle-socioeconomic class families living in New Delhi and randomly assigned to receive placebo, vitamin B12, folic acid, or vitamin B12 and folic acid supplements for a period of 6 months (105). The intervention was a lipid-based nutritional supplement prepared by Nutriset, Ltd (Malaunay, France). Children were supplemented with 1 spoon (5 g) if they were 6 to 11 months, and 2 spoons (10 g) if they were ≥12 months. Each 10 g of the supplement (dose for children aged ≥12 years) contained 54.1 kcal total energy, 0.7 g of protein and 3.3 g

of fat. For the groups that were assigned to receive B vitamins, the supplement also contained 1.8 µg of vitamin B12 or 150 mg of folic acid or both, constituting 2 recommended daily allowances (105). Trained field supervisors measured weight and length at the time of enrolment (i.e., child age range of 6-30 months) and after six months of supplementation (i.e., at age range of 12-36 months).

Study procedures in the follow up study

The follow up study aimed to examine the long-term effects of the 6-month supplementation of vitamin B12 and/ or folic acid in early childhood on cognition at age 6 to 9 years (106). An attempt was made to contact all the children that had completed the parent trial which enrolled 1000 infants and young children. Contact was established with 798, of which 791 consented to participate. Information was collected on socio-economic status of the families of these children. Height, using Seca 213 scale and reading to the nearest of 0.1cm; and weight, using Digitron scales to the nearest of 50 g, were measured in the follow up study (i.e., at age range of 6-9 years) by trained and standardized study team members.

The cognitive assessments were conducted at the study clinic by trained psychologists. Ten percent of all assessments were double scored, attaining an agreement of above 96%. Wechsler Intelligence Scale for Children 4th edition (India) (WISC-IV^{INDIA}) was used to assess general intellectual ability (Intelligence Quotient, IQ) (107). This version has Indian norms and is validated for the Indian population. Seven subtests were conducted, and their scores were summed up to three index scores; the Perceptual Reasoning (Block design, Picture concept, Matrix reasoning), Processing Speed (Symbol search, Letter-number sequences) and Working Memory (Digit span, Coding) (107). Because verbal comprehension tests in the WISC-IV^{INDIA} require English language skills, this component was substituted with the Crichton Vocabulary Scales (CVS) to assess verbal skills (108). The CVS has been translated to Hindi and has Indian norms providing a standard total score. Seven age-appropriate subtests from the neuropsychological test battery (NEPSY-II) were also included: Inhibition, Design

Fluency, Word Generation, Visuomotor Precision, Manual Motor Sequences, Affect Recognition and Geometric Puzzles (109).

Study 3: Early child stimulation, linear growth and neurodevelopment in low-birth-weight infants

Study design and site

This secondary data analysis was conducted using data from an individually randomized controlled trial aimed to evaluate the effect of community-initiated Kangaroo Mother Care (ciKMC) on neurodevelopmental outcomes of infants born low birth weight at 12 months of corrected age (110). The study was conducted in resource constrained settings of rural and semi-urban Haryana, North India.

Study subjects, interventions, and outcome assessment in the parent trial

A total of 552 stable preterm or small for gestational age term infants weighing between 1500 and 2250 g were identified within 72 hours of birth and included in the trial and followed up till 12 months of age (110). As per the government recommendations, infants weighing between 1500-1800 gm were initially referred to a health facility for evaluation. These infants were considered for inclusion only if the families refused to take the baby to the health facility, if the baby was taken but the medical doctor/paediatrician did not recommend admission, or if admission was done, it was for less than 72 hours. Infants who were unable to feed, had difficulty in breathing, had less than normal movements, and those with gross congenital malformations were excluded. As this was a trial assessing the efficacy of Kangaroo Mother Care (KMC) initiated at home/community, those infants who had KMC initiated at the health facility were excluded (110).

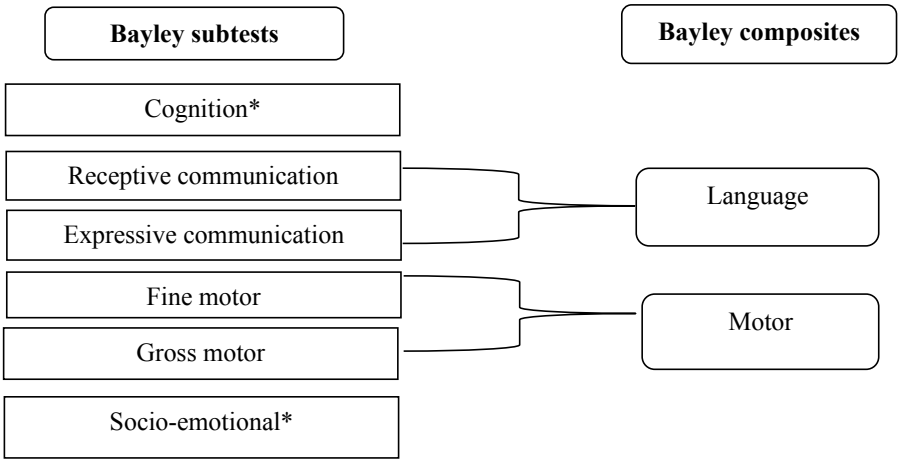
Baseline information was collected on maternal and paternal age and education, birth order, parity and sex of the infant. Gestational age was documented from an ultrasound report, hospital records or maternal recall, whichever was available, in the given order of preference. The wealth of the family was determined by an index created through a

principal component analysis based on household assets (111). Information on vital status, illnesses (including any hospitalization) along with anthropometric measurements (weight and length) were captured by an independent trained team during their home visits at infant age 1, 3, 6 and 12 months. Caregivers were asked about illness(es) and hospitalization(s) in the 2 weeks preceding the visit. Length was measured using infantometers reading to the nearest 0.1 cm. Exclusivity of breastfeeding was assessed at 1, 3 and 6 months of infant age through a structured questionnaire. Developmental outcomes were ascertained in the study clinic by trained psychologists using BSID-III at 12 months of corrected age (98,99). Child stimulation at home was assessed at 12 months of age by trained psychologists using PROCESS questionnaire (103,104).

Description of the neurodevelopment assessment tools used in the three studies

Bayley Scales of Infant and Toddler Development (BSID), 3rd edition (used in Study 1 and Study 3): This is a comprehensive assessment tool of developmental functioning in infants and toddlers aged 1-42 months (98,99). The tool is directly administered to the child to assess cognitive, language and motor development whereas socioemotional and adaptive behaviour is assessed using parent/caregiver completed rating scale. The scores are reported either as scaled scores (mean 10, SD 3; range 1 to 19) or as composite scores (mean 100, SD 15; range 40 to 160). The figure below shows the structure of the Bayley-III tool.

Figure 1. Bayley-III Structure



*Composite score equivalents available

Adaptation

We did adaptations, prior to using BSID-III, in the study settings (110). For the adaptation, the test items were reviewed by the team of psychologists with respect to their cultural relevance. Subsequently, necessary modifications were identified, discussed and incorporated. While conducting the adaptations, care was taken to match the style of the original item. For items that required translation in the local language i.e., Hindi, the translation was done by psychologists fluent in the local language and with a thorough understanding of the cultural context. An individual that was not a part of the study team, performed the back-translation. Prior to the start of the formal testing, the adapted materials were piloted on approximately 15–20 infants and children. In the two studies where this tool was used, standardization exercises were conducted both prior to and during the conduct of the assessments. The resultant inter-rater agreement was excellent (Intraclass correlation, ICC ranged between 0.92-0.99).

Infant temperament scale (ITS): It was used to assess infant temperament. It is a parent reported measure containing 47 items that assess 6 dimensions (activity, positive emotionality, negative emotionality, sociability, attention and soothability) (100). Items are designed to be answered by the parent/caregiver using a five-point scale ranging from "my child is always like this" to "my child is never like this" [01 = my child is always like this; 02 = my child is like this most of the time; 03 = my child is like this half of the time; 04 = my child is like this less than half of the time; 05 = my child is never like this]. Higher scores on ITS reflect more difficult temperament.

Background of the ITS tool used

We did not have a validated tool to measure infant temperament that was relevant for use in our study context. We, therefore, used the scale that also was used in the "The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health" (MAL-ED) study (100,112). This was a large community based observational study that aimed to understand the link between gut infection and occurrence of malnutrition and consequent growth faltering, neurodevelopmental deficits and sub-optimal immunogenicity of childhood vaccines

(112). The MAL-ED study adapted the ITS that was developed by Dr Theodore Wachs for research purposes in Peru. The original version of the scale contained 112 items. These items assessed 8 dimensions of temperament: activity, positive emotionality, negative emotionality, sociability, fear, attention, cooperativeness, and soothability (100). During the pilot use of the scale, the MAL-ED investigators felt the need to drop two dimensions (fear and cooperativeness), mainly to make it more feasible to administer it as the original scale was lengthy and time consuming (100). There was a total of 47 items in the final adapted tool that assessed 6 dimensions.

Pendergast et al examined the validity of this adapted version for measuring infant temperament (113). The study utilized data from 1933 infants included in all 8 sites of the MAL-ED study (India, Pakistan, Bangladesh, Nepal, Brazil, Peru, South Africa and Tanzania). Based on their findings, the authors suggested that ITS could be used to measure certain aspects of temperament in young children across many cultural backgrounds. On the contrary, use of this tool to assess some dimensions of temperament (such as activity and soothability) across multiple cultural groups may need further research (113).

Child Behavior Checklist- preschool (CBCL): This tool was used to assess behavioural problems. This is a caregiver reported tool intended for children aged 18 months to 5 years (101). It consists of 100 items, where the responses are recorded on a Likert Scale [0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True]. The distribution of these 100 items is under 8 problem categories:

1. Emotionally Reactive
2. Anxious/Depressed
3. Somatic Complaints
4. Withdrawn
5. Sleep Problems
6. Attention Problems
7. Aggressive Behaviour
8. Other Problems

These problems are further summed to provide a score for internalizing (emotionally reactive, anxious/depressed, somatic complaints and withdrawn) and externalizing (attention problems and aggressive behaviour) problem scales. A total score from all questions is also derived by adding up the internalizing scores, externalizing scores, other problems and sleep problems. For each problem scale and the total score, the raw scores are converted into t-scores. An increasing t-scores indicate the behavioural problems in a child (101). The scores are based on US-norms.

"Pediatric Review of Children's Environmental Support and Stimulation (PROCESS)" questionnaire: This is a parent/caregiver reported tool and was used to measure environment at home and child stimulation by caregivers at 12 months of age (102,103). This could be administered either in a clinic or in a home setting. In this study, it was administered by trained psychologists in the study clinic. It consists of three components: a parent questionnaire (22 items), clinical observation (20 items), and a toy checklist (40 items). The parent questionnaire includes items about the physical environment, household organization, and stimulation practices for development. The clinical observational items are related to the emotional quality of parent-child interactions and the toy checklist is for the number of toys the child possess. Total scores are summed across the three sections and higher scores reflect better infant stimulation and support. The tool was used after adapting according to the local cultural context, translating into local language (Hindi), and pre-testing for use.

Home Observation for Measurement of the Environment (HOME) tool: It was used for assessing home environment and stimulation at 24 months of age (104). It consists of 45 items with responses coded at either 0 (not observed/reported during visit) and 1 (observed/reported during visit). The items are grouped under the following 6 categories:

Responsivity	Assesses how well the parent responds to the behaviour of the child and communicates freely with the child through words and actions.
Acceptance	Assesses parental acceptance of less-than-optimal behaviour from the child and the avoidance of undue restriction and punishment

Organization	Assesses the extent to which the parents have maintained a regular and predictable daily schedule of the family and of the child and ensured safety of the child's physical environment
Learning materials	Assesses whether there is a provision of appropriate play and learning materials that are capable of enhancing development
Involvement	Assess the extent to which the parents actively participate in the child's learning and provides stimulation for increasingly mature behaviour
Variety	Assesses whether there is a provision for inclusion in daily life of people and events that bring some variety (without disorganization) into the child's life.

Higher scores reflect better stimulation and support to infants. The tool was used after adapting according to the local cultural context, translating in local language (Hindi), and pre-testing for use.

WISC-IVINDIA; Wechsler Intelligence Scale for Children 4th edition (India): It was used to measure the general intellectual ability (Intelligence Quotient, IQ). This version has Indian norms and is validated for the Indian population (107). It consists of seven subtests and the scores within these sub-tests were summed up to three index scores: the Perceptual Reasoning (Block design, Picture concept, Matrix reasoning), Processing Speed (Symbol search, Letter-number sequences) and Working Memory (Digit span, Coding). The administration time is 60-90 minutes, and this test can be used in children aged 6 to 16 years, 11 months (107).

Crichton Vocabulary Scale (CVS): This is used for assessment of verbal comprehension and is available in the local language, Hindi and has Indian norms (108). The tool is relevant for children aged 4 to 11 years and administration time is around 30 minutes.

Neuropsychological test battery (NEPSY-II): It is used to assess neuropsychological development in children aged 3 to 16 years under the following domains i.e., attention and executive function, language, memory and learning, sensorimotor, social perception and visuospatial processing (109). The administration time is 45-60 minutes. The scores are based on US- norms.

Statistical analysis

A detailed statistical analysis plan was made in consultation with the co-authors prior to starting the analysis. Baseline characteristics were described using summary measures with measures of dispersion such as mean with standard deviation, median with interquartile range, and percentage, as appropriate.

Study 1: Milk-cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomized controlled trial in India

The primary analysis included the comparison of neurodevelopment outcomes at 12 and 24 months of age between the three study groups (high protein group, modest protein group and no supplementation group) and was based on the intention-to-treat principle. The outcomes were continuous and therefore, the effect sizes (difference in means and 95% confidence intervals, CIs) were calculated using generalized linear models (GLMs) of the Gaussian family with an identity-link function. The primary analysis was unadjusted as there were no substantial differences in the baseline characteristics among children in the three groups. Additionally, an adjusted analysis was conducted after including variables in the models that have been shown to influence neurodevelopment outcomes, based on previously published studies. Generalized estimating equation (GEE) model was used to adjust for repeated measurements when the outcomes were measured more than once in each the child. GEE model of the Gaussian family with an identity-link function and an autoregressive covariance-variance matrix that factored in time was used. A subgroup analysis was conducted with infants who were stunted (LAZ<-2) at the time of enrolment.

Study 2: Linear growth between early and late childhood and cognitive outcomes at 6 to 9 years of age

The exposure i.e., HAZ was calculated based on the WHO Child Growth Standards, using the "zanthro" package in STATA (114). A combined WISC-IV^{INDIA} and CVS z-score was calculated based on converted z-scores for the three index scores in the WISC-IV^{INDIA} (the Perceptual Reasoning, Processing Speed and Working Memory) and the

total CVS score. A combined NEPSY-II z-score was calculated based on converted z-scores in seven subtests (Inhibition, Design Fluency, Word Generation, Visuomotor Precision, Manual Motor Sequences, Affect Recognition and Geometric Puzzles).

In order to understand the association between change in HAZ scores (from baseline, i.e., at ages 12-36 months to follow up i.e., at 6-9 years) as the exposure and cognitive test scores at follow up (i.e., at 6-9 years) as the outcome, a multivariable linear regression was performed. A purposeful selection of covariates was done for adjustment in the models (115,116). First, a univariate analysis was run with change in HAZ score as the exposure and cognitive test scores as the outcome and the resulting beta-coefficient was noted. Thereafter, each of the covariates was added in the model, one by one, and the change in beta-coefficient was noted. To improve the chances of retaining meaningful confounders, all covariates that brought at least 15% change in the beta-coefficient were included in the multivariable model.

Stunting was defined as HAZ <-2, based on the standard WHO definition (117). Four categories of "change in stunting status" were created i.e., *persistently stunted* (stunted both at baseline and at follow up, considered the reference); *never stunted* (not stunted at baseline and follow up); *recovered* (stunted at baseline and not stunted at follow up); *faltered* (not stunted at baseline and stunted at follow up). Multivariable linear regression models were developed with "change in stunting status" as the exposure and cognitive test scores as the outcome. As described earlier, a purposeful selection of covariates for adjustment in the model was performed. The interaction between change in stunting status and baseline HAZ score was also assessed. In the absence of a significant interaction, a third model was created where adjustment for baseline HAZ scores was done. A generalized additive model (GAM) analysis was performed to generate perspective plots to visually present the relationship between baseline HAZ score, change in HAZ score and the cognitive z-scores.

Study 3: Early child stimulation, linear growth and neurodevelopment in low-birth-weight infants

The LAZ was calculated based on the WHO Child Growth Standards (114). Stunting was defined as LAZ <-2, based on the standard WHO definition (117). Data on length were available for 1, 3 and 6 and 12 months of infant age. PROCESS scores, reflecting stimulation environment at home, were measured at 12 months of age and categorized into three groups: *Low stimulation group* (< Mean-1SD); *moderate stimulation group* (Mean ±1 SD) and *high stimulation group* (> Mean + 1SD).

We assessed the interaction between LAZ scores at 6 months of age and the PROCESS scores at 12 months using the likelihood ratio test comparing models with and without the interaction terms. Analyses were stratified following the identification of a possible interaction. We initially did a screening where a P-value for interaction of less than 0.20 was investigated further (118). The investigation was focussed on examining whether the magnitude of association between LAZ and outcome(s) of interest differed between the PROCESS score categories. Stratified results were presented at differing levels of PROCESS scores (low, moderate and high stimulation). For each of the categories of the PROCESS score, we used linear regression with the composite scores for cognition, motor or language as an outcome and LAZ score as the exposure variable. Selection of variables for adjustment in the models was based on biological plausibility and purposeful selection principle (115,116).

Similarly, to assess whether the association between PROCESS scores and neurodevelopmental outcomes was modified by whether the babies were stunted or not, the interaction between the PROCESS score categories and stunting status was assessed. In instances where the P-value of interaction was less than 0.20, the analyses were stratified and the effect sizes for the association between PROCESS categories and outcome(s) of interest were presented by the stunting categories. We used GAM in the *mgcv package* in R statistical package to depict non-linear associations between PROCESS score, LAZ and outcome scores (composite cognitive, motor and language scores).

Ethical approvals and trial registration

The nutritional supplementation trial (study 1) and follow-up studies whose data were utilized for study 2 and study 3 had obtained approval from the institutional ethics committee of Society for Applied Studies (India) and from the Norwegian Regional Committee for Medical and Health Research Ethics (REK Vest). The primary trial whose data were utilized for Study 3 also had ethical clearances from the WHO Ethics Review Committee.

Protocol for study 1 (CTRI/2019/03/018238) and the follow up study whose data were utilized for study 2 (CTRI/2016/11/007494) were registered at Clinical Trials Registry-India. The parent trial whose data were utilized for study 3 was registered at clinicaltrials.gov (NCT02631343). In all the studies involving collection of data from children and/or their caregivers, written informed consent was obtained. The informed consent forms were translated into simple local language (Hindi) that could be easily read and understood. In instances where the caregiver(s) was unable to read, the consent form was being read out by the study team member before obtaining consent. In those who were unable to sign, a thumb imprint was taken which was witnessed (counter signed) by an impartial literate witness. Funding bodies did not have any influence on the study design, implementation and analysis of the data.

RESULTS

Summary of the key findings from the three studies

	Paper 1	Paper 2	Paper 3
Key findings	*At 12 months of age* Compared to infants in the "no supplement" group, an increase in the motor scores and a decrease in the infant temperament scores was observed in the infants from the modest protein group Infants in the high protein group had lower socio-emotional scores and higher scores on infant temperament scale when compared to modest protein group. *At 24 months of age* No significant differences observed in any of the neurodevelopment scores between the three study groups	HAZ in the first two years was significantly associated with both the WISC-CVS and the NEPSY-II z-score at 6-9 years of age. There were no significant associations between change in HAZ scores between early and late childhood and WISC-CVS or NEPSY-II z-scores.	Interactions were observed between LAZ and PROCESS score categories for cognitive, motor and language outcomes. In the low stimulation group, the adjusted regression coefficient for the association between LAZ and cognitive score was substantially higher than in the moderate and the high stimulation group. Similar pattern was noted for the motor and language score.
Conclusions	There may be a short-term benefit of supplementation with modest amount of protein and multiple micronutrients, but not high amounts of protein, on the motor scores and infant temperament.	Linear growth between early and late childhood is not associated with cognitive outcomes at ages 6 to 9 years.	Moderate to high quality stimulation may alleviate the risk of poor neurodevelopment in LBW infants with linear growth deficits

Study 1: Milk-cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomized controlled trial in India

The parent trial assessed the impact of milk-cereal mix supplementation, from 6 to 12 months of age, on linear growth at 12 months in a total of 1548 infants (97). From these, 1134 infants were assessed for their neurodevelopment at 12 months and 1214 children at 24 months of age (94). The proportion of infants consuming milk–cereal mix on >75% of days of the 180 days supplementation period was >80% for both modest-protein and high protein group. The proportion of infants who consumed IFA for >75% of days was around 70% for the three groups. The baseline characteristics of the children assessed for their neurodevelopment at 12 and 24 months of age were statistically similar across the three groups.

For assessments at 12 months, compared to no supplement group, there was an increase in the motor scores in the modest protein group (mean difference, MD 1.52, 95% CI: 0.28, 2.75) but not in high protein group (MD 0.77, 95% CI: -0.53, 2.06). No difference in motor scores was noted for comparison between modest and high protein groups. There were no significant differences in the cognitive and language scores for any of the three comparisons i.e., modest protein vs. no supplement group, high protein vs. no supplement group and modest vs. high protein group. Those in high protein group had lower socio-emotional scores when compared to modest protein group (MD -1.40, 95% CI: -2.43, -0.37). Analysis of infant temperament scale scores revealed lower scores for modest protein group compared to no supplement group (MD -2.76, 95% CI: -4.23, -1.29) and higher scores for high protein group compared to modest protein group (MD 2.05, 95% CI: 0.62, 3.48).

For assessments done at 24 months of age, there were no significant differences in the cognitive, motor, language and socio-emotional scores as well as in the scores for internalizing behaviour, externalizing behaviour and total problem for any of the three comparisons. In the GEE analysis, compared to no supplement group, only children in the modest protein group had some improvement in their motor scores over the 12

months follow-up period (i.e., from 12 to 24 months of age) (MD 0.98, 95% CI: 0.06, 1.91).

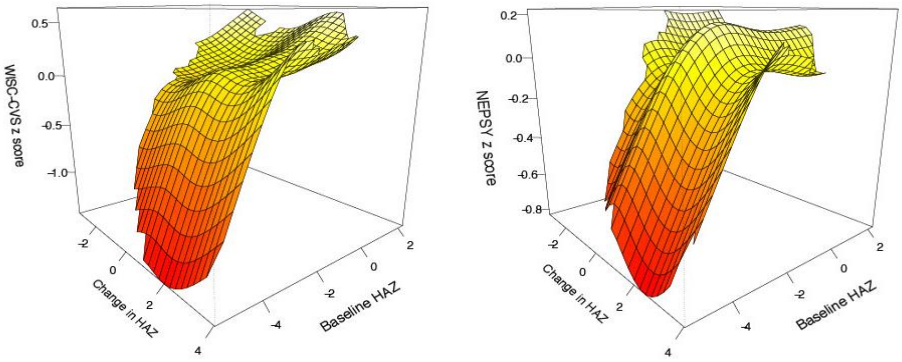
The subgroup analysis among infants stunted at the time of enrolment in the trial suggested a significant beneficial effect in modest protein group, compared to no supplementation group, on cognitive, motor and language scores at 12 months of age. Compared to infants in the modest protein group, those in the high protein group had significantly lower cognitive, language and socio-emotional scores at 12 months of age. No differences were observed in cognitive, motor, language and socio-emotional scores among the three groups at 24 months of age.

Study 2: Linear growth between early and late childhood and cognitive outcomes at 6 to 9 years of age

Follow up data from 773 children were analysed (95). The mean (SD) follow-up period was 5.95 (0.24) years and age of children at the time of follow up assessments was 7.83 (0.65) years. HAZ in the first two years of life was significantly associated with both the WISC-CVS [standardized beta coefficient (ß) 0.15, 95% CI: 0.08, 0.23], and the NEPSY-II z-score [ß 0.09, 95% CI: 0.03, 0.18] at 6-9 years of age. Multivariable linear regression models did not show a significant association between change in HAZ scores and the WISC-CVS [ß -0.03, 95% CI: -0.11 to 0.04] or the NEPSY-II z-scores [ß -0.04, 95% CI: -0.12 to 0.06]. The GAM plots (Figure 2) depicted the relation between baseline HAZ, change in HAZ and WISC-CVS z-score or NEPSY-II z-score and showed that WISC-CVS z-score or NEPSY-II z-score increased with an increase in baseline HAZ whereas the change in HAZ did not affect these scores.

Out of the 773 children included in the analysis, 13.1% were in the persistently stunted (n=101) category; 56.0% were in never stunted (n=433) category; 30.0% were in the recovered (n=224) category and the remaining around 2% were in the faltered (n=15) category. In the multivariable model, recovery from stunting was not associated with higher WISC-CVS z-score [ß 0.15, 95% CI: -0.05, 0.34] and NEPSY-II z-score [ß 0.17, 95% CI: -0.05, 0.39] when compared to children who were persistently stunted.

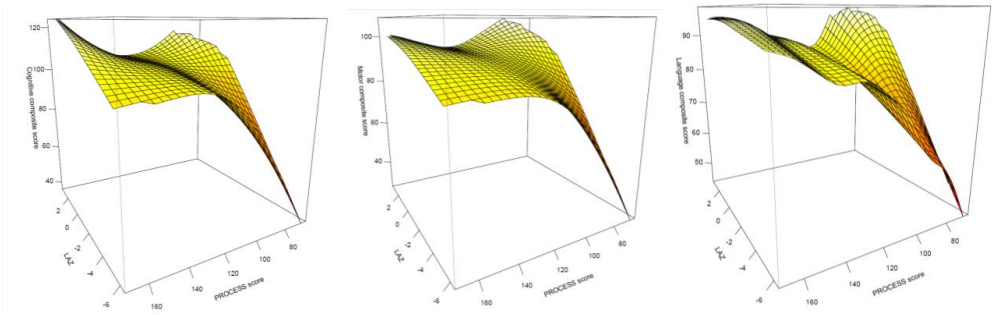
Figure 2. GAM plot showing the relation between baseline HAZ score, change in HAZ score from early to late childhood and WISC-CVS and NEPSY z-scores



Study 3: Early child stimulation, linear growth and neurodevelopment in low-birth-weight infants

Data for analysis was available from 516 low-birth-weight infants (96). Potential interactions were observed between LAZ and PROCESS score categories for cognitive (interaction P-value=0.08), motor (interaction P-value=0.03) and language outcomes (interaction-value=0.12). In the low stimulation group, the adjusted regression coefficient (*b* = 3.63, 95% CI; 1.22, 6.03) for the association between LAZ and cognitive score was substantially higher than in the moderate stimulation (*b* = 1.41, 95% CI; 0.25, 2.56) and the high stimulation group (*b*= 1.69, 95% CI; -1.15, 4.52). Similarly for the motor and language score, in the low stimulation group, the adjusted regression coefficient was higher than in the moderate stimulation and the high stimulation group. In both stunted and non-stunted infants, PROCESS scores were significantly associated with cognitive, motor and language scores with a clear dose response relationship. However, the adjusted regression coefficient was comparatively higher in stunted infants. The GAM plots supported the findings obtained in regression models (Figure 3). These plots showed that at lower PROCESS scores, the cognitive, motor and language scores decreased with decrease in LAZ scores. Further, with an increase in the PROCESS scores, the neurodevelopment scores increased, more so in those with LAZ <-2.

Figure 3. GAM plot depicting the relationship between length-for-age Z score, PROCESS score and cognitive, motor and language composite score



DISCUSSION

Overall Summary of the findings and comparison with previous literature

On a broader level, the findings of the thesis confirms that child neurodevelopment is influenced by multiple risk factors. These risk factors could also interact and modify each other's strength of association with the neurodevelopmental outcomes. Consequently, the "one size fits all" approach may not be appropriate, wherein, a standardized approach is applied to address a particular health issue across a population, regardless of individual differences. While this approach can be effective in certain cases, it may not be the best approach when it comes to improving child development outcomes. This is because child development is influenced by a variety of factors, including genetics, environment, and cultural background. Therefore, the interventions that are most effective in promoting positive child development may differ depending on the specific needs and circumstances of each child. In order to yield the desired improvements in child development, public health interventions need to be tailored to the specific needs and circumstances of each child and their families. This requires a more individualized and flexible approach.

The findings of the thesis respond to some of the important public health gaps in childcare in low-middle-income settings. The evidence from the nutritional supplementation trial suggests that supplementation with modest amount of dairy protein and MMN may lead to short term small improvements in motor function and infant temperament. However, it also highlights the need to be careful while supplementing with higher amounts of dairy protein as this was found to be associated with lower socio-emotional scores and a difficult temperament. In the secondary data analyses, we found that linear growth in the first 24 months, but not beyond that, was associated with cognitive and executive function scores in late childhood. Particularly during infancy and among LBW infants, the association of linear growth with neurodevelopmental scores was seen to be influenced by the quality of child stimulation and nurturing care available at home. We found that with higher levels of stimulation and nurturance at home, the association between LAZ and neurodevelopmental scores was attenuated. This probably meant that a high-quality home environment may alleviate the risk of poor development

scores in LBW infants with linear growth deficits. The relevant findings of the three studies included in this thesis have been discussed further in relation to the available literature.

Effect of protein and micronutrient supplementation on neurodevelopmental outcomes

Immediately after completion of 6 months of supplementation, we found that infants receiving milk-cereal mixes with modest amount of protein and MMN had a better motor score and favourable temperament, compared to those that did not receive any supplementation. Further, those receiving milk-cereal mix with higher amounts of protein had lower socio-emotional scores and a more difficult temperament, when compared to infants receiving mixes with modest protein. We also found a significant beneficial effect of supplementation with modest amount of protein and MMN among stunted infants on cognitive, motor and language scores. One year after stopping the supplementation, we found no significant differences in the cognitive, motor, language and socio-emotional scores as well as in the scores for problem behaviours for any of the three group comparisons.

Existing direct evidence on the effect of protein supplementation during infancy on neurodevelopment is limited. Previous studies have examined a wide range of children, and this limits comparability (119-121). Our findings are similar to a recent systematic review and individual participant data meta-analysis that found a modest improvement in motor, language and socio-emotional scores in children, aged 6-24 months, receiving small quantity lipid-based nutritional supplement (SQ-LNS) (47). The nutritional composition of SQ-LNS was similar to the milk-cereal mix provided to infants in the modest-protein group in our study. The review also found an enhanced effect of supplementation in populations with high burden of stunted children (47). Our study also found that supplementation with high amounts of protein was not favourably associated with certain aspects of child development. Some studies among high-risk infants observed an association between high protein supplementation in the very early half of infancy and neurodevelopment impairment at around 24 months of age (122,123).

However, it still needs to be tested conclusively whether such an association is causal, and if yes, the potential underlying mechanisms need to be identified.

There are few explanations for not observing effects of protein supplementation on neurodevelopment in our study. First, the intervention was confined to the second half of infancy whereas studies that have shown an impact of supplementation covered the periods of pregnancy, lactation and early childhood (80,124,125). Second, the duration of supplementation was relatively short i.e.,180 days and did not cover the critical period of 24 months entirely. Third, we assessed neurodevelopment at 12 and 24 months of age whereas most studies that noted an improvement conducted assessments in late childhood (119,121). It is well known that brain development tends to be more stable as the age increases and therefore, any significant effect of an intervention can be reliably detected at later ages (126,127). Further, it is important to consider that child neurodevelopment is affected by multiple factors, with nutrition being one of them. Therefore, holistic investments aimed at adequate nutrition, prevention of severe morbidities and promotion of responsive care and learning opportunities are required (128).

Linear growth between early and late childhood and cognitive outcomes at 6 to 9 years

We found linear growth in the first 2 years to be associated with cognitive outcomes assessed in late childhood. We also observed that change in linear growth (reflected as change in LAZ) from 2 years onwards till the late childhood were not associated with cognitive scores at 6-9 years of age. Our findings are similar to a recent meta-analysis that documented a positive association between linear growth in the first two years of life and cognitive development among children in LMICs (39). On the other hand, findings contrast with some of the studies that showed improvement in linear growth and/or recovery from early stunting to be associated with improved cognitive outcomes (68,60,129). A critical difference between these studies and our study is related to the adjustment of baseline length-for-age z score. The previous studies did not adjust for baseline LAZ whereas we did. There is available literature suggesting the potential of

introducing “regression-to-the-mean” bias when adjusting for baseline in analysis of change and indicating that baseline adjustment substantially alters the effect size (130). We, however, conducted the analyses with and without adjustment for baseline LAZ scores. Both these analyses suggested that increments in LAZ scores from baseline till follow up were not associated with higher cognitive scores.

The findings allude to the possibility of a substantial overlap among factors that influence both linear growth and neurodevelopment during early childhood. These factors may include breastfeeding, complementary nutrition, morbidities including diarrhoea and pneumonia and responsive and nurturing care (63). Another emerging possibility is that the factors that affect linear growth and neurodevelopment in later childhood may either not be similar or they have a differential effect on these outcomes. The meta-analysis by Prado et al seems to support this possibility (46). This meta-analysis included studies among under-five children and showed that nutritional interventions alone led to modest improvements in linear growth but were associated with only small improvements in child development (46). Nurturing and stimulation interventions had significant effects on child development but no effects on linear growth. The review concluded that the determinants of linear growth and neurodevelopment are only partly shared and that improved linear growth may not necessarily be associated with improved cognition (46).

Linear growth and child stimulation influencing each other’s individual association with early child development

In this study, we found that that with increase in quality of stimulation and nurturance at home, the association between linear growth and neurodevelopmental outcomes attenuated. We also observed that the association of stimulation at home with neurodevelopmental outcomes was stronger in stunted than non-stunted infants. Our findings support the studies conducted in India, Vietnam, Burkina Faso, Malawi and Ghana where among non-low birth weight children, a nurturant home environment was observed to attenuate the association between linear growth and neurodevelopmental outcomes (62,71,72). On the other hand, studies among the Malaysian and Jamaican

children found no significant influence of quality of home environment on the association between linear growth and cognitive outcomes (73,74). We believe that this discrepancy may be due to smaller sample sizes in these studies, which limited the power to detect significant interactions. Our findings support the promotion of stimulation to LBW infants in order to offset the negative effect of growth faltering on neurodevelopmental outcomes.

Methodological issues

Validity and precision are key attributes of the findings from an epidemiological study. The validity is usually categorized into internal and external validity (131). Internal validity is an indication of whether the design of the study, the procedures used, the way the study was conducted, and the analysis of data answers the research question under consideration without any evident bias (131). External validity usually indicates whether the findings of the study can be applicable to contexts, apart from where the study was conducted (131). Selection bias, measurement bias and bias due to confounding are important contributors to violations of internal validity (132,133). Precision refers to the magnitude of variation between sample statistics and depends on the sample size, variability and random errors (134). Some measures that are indicative of precision are standard deviation and confidence interval.

Selection bias

Selection bias usually occurs when the sample of subjects studied is systematically different from those who were not included in the study. Defining a clear inclusion and exclusion criteria and attempting to reduce the loss to follow up/attrition rate largely reduces the risk of selection bias (135). In all the three studies that are included as part of the thesis, the possibility of selection bias seems low.

In the randomized controlled trial that assessed the impact of nutritional supplementation on neurodevelopment at 12 and 24 months of age, there were clear inclusion criteria. At 12 months, 1134 infants (out of the required 1200) were assessed i.e., loss to follow up rate of ~5%. We were unable to contact these 5% infants as the family had temporarily

moved out of the study area at the time of scheduled assessment. These children were contacted during the follow up in their 2nd year of life and neurodevelopmental assessments were done at 24 months. At 24 months, the required sample size of 1200 was achieved.

In the secondary data analysis to understand the association between linear growth change between early and late childhood and cognitive outcomes at 6 to 9 years of age, follow up data of 791 children, out of the 1000 children that had previously participated in a randomized double-blind placebo-controlled trial, were utilized. We were able to contact around 80% of the children from the original cohort, after a period of around 5 years. In another secondary data analysis aimed at understanding the extent to which linear growth and early child stimulation modify each other's association with neurodevelopmental outcomes among low-birth-weight infants, data from 516 infants at 12 months of age were utilized, out of the parent trial study sample of 552 i.e., loss to follow up rate of ~6%. The baseline characteristics of the infants administered neurodevelopment assessment was similar to those enrolled in the primary trial.

Measurement error

It is also referred as observation or experimental error and is defined as the difference between the observed and the true value of the variable being measured (136). This is broadly of two types: random and systematic error. Random errors reflect the "chance" difference whereas systematic error indicates a consistent difference (in the same direction) between observed and true value (137,138). While random errors could occur naturally in any experiment and usually do not pose a threat to the validity of the findings, the systematic errors pose a concerning problem as they affect the accuracy of the measurements and can bias away from the true value, thereby, leading to false interpretations.

Random error in the context of the studies included in the thesis

We acknowledge that there is a possibility of random errors in both exposures and outcome measurements. For all the three studies, we had an adequate sample size which

might help in minimizing the effect of random measurement error in outcome variable. Further, while we used standard precise equipment for anthropometric measurements (for length/height, to the nearest of 0.1 cm and for weight, to the nearest of 50g), data collection for other relevant exposures such as quality of child stimulation at home and compliance to nutritional supplementation relied on less objective measures which may have introduced random errors. Such errors in exposure measurement could bias the effect estimates towards the null and such an occurrence is often known as "attenuation or regression dilution bias" (139).

Systematic error in the context of the studies included in the thesis

We expect minimal systematic error because of the comprehensive standardization and periodic re-standardization exercises for the team involved in measurement of exposures, process indicators and growth as well as neurodevelopmental outcomes. We adapted tools for our study setting prior to using it. An independent team of trained and standardized psychologists conducted all the neurodevelopmental assessments. The standardization exercises were conducted prior to start of the study and periodically during the conduct of the study. Similar procedures were adopted for the growth-related measurements. Standard calibrated scales were used for anthropometric measurements.

The use of neurodevelopmental tools in the three studies merit further discussion. We had used globally accepted standard assessment psychometric tools after adaptation to suit local context. Most of the tools used derive their standards from sample of children tested in high-income settings. There is a possibility that, these standards, when applied to infants and children in our study, may have led to scores that may not indicate their actual developmental function i.e., the validity of the neurodevelopment scores obtained may be compromised. In the RCT (i.e., study 1), this may not have impacted the findings to a larger extent as the deviations in neurodevelopment scores is expected to be similar in all the three groups. In the other two studies (i.e., study 2 and 3), the secondary data analysis was aimed at understanding an association between exposure(s) of interest and neurodevelopment scores. We expect that while the direction of association observed may not be impacted, the strength of association may not reflect the true estimate.

Confounding, adjustment of variables and interaction

Confounding can be defined as an inaccuracy in the observed association between an exposure and outcome due to presence of a variable (called as confounder) that has the ability to influence both the exposure and the outcome of interest (140,141). It is commonly noted in observational studies and in secondary analyses. In our randomized controlled trial, we did not adjust for any variable in the statistical model as we did not note any baseline differences in the socio-demographic and familial characteristics between the three study groups. In the other two manuscripts that used secondary data for analysis, we were careful during the selection of variables for adjustment in the regression models and followed the principle of purposeful selection of variables as suggested by Hosmer and Lemeshaw (116). The key advantage with this approach is that it provides a systematic way for selection of potential confounding factors. It should, however, be considered that this approach was developed to identify predictors for a dependent outcome and not to adjust for confounding in the model aimed at understanding the association between a particular exposure and outcome.

We acknowledge that in spite of our efforts to account and adjust for confounding, there is a modest possibility that residual confounding may have existed. We did not have information on some of the important factors such as child morbidities, gestational age, and dietary intakes of the child (both in terms of calories and essential micronutrients). They may act as confounders in the pathway associating linear growth with neurodevelopmental outcomes. It is also important to note that even if we would have had data for a particular confounding variable, any misclassification or random errors for the variable may also have resulted in residual confounding (142).

An important issue, especially in the context of study 3, is the consideration of P-value to determine presence or absence of interaction. The analysis in this study was related to assessing the interaction between LAZ and child stimulation scores (using PROCESS) for neurodevelopment outcomes at 12 months of age. There is lack of consensus with regards to which P-value to consider for suggesting presence of an interaction. While some propose to adhere to the conventional P-value of <0.05, others suggest considering

a P-value of <0.20 as the power to test for interactions is usually low in many epidemiologic studies (143-145). Some researchers further suggest that P-value based assessments of interaction should be combined with stratum-specific measures and prior biological knowledge (146,147). In our study, we considered a P-value of less than 0.20 to further investigate for potential interaction. Subsequently, we considered the magnitude of effect size within the subgroups and made careful interpretations.

External validity

The three studies were conducted in low resource settings in India and had a fairly strict inclusion and exclusion criteria. The findings could, therefore, only be generalized to other low-middle-income settings that experience similar constrained environment characterized by low socio-economic status and high burden of child undernutrition and micronutrient deficiencies. One of the studies was conducted in infants born with LBW i.e., a weight of 1500-2250 g within 72 hours of birth and therefore, the findings could be applicable only to LBW infants.

Strengths

The main strength of the thesis is the use of good quality data from RCTs conducted in community settings. The loss to follow up rates were lower i.e., around 5-6% for the studies involving a short follow up period of around 12 months and nearly 20% for those requiring follow up of >5 years. Wherever applicable, the primary studies had high compliance to the intervention and the data collection on most of the exposures and outcomes of interest was done by a highly trained and standardized team. Especially, the neurodevelopment assessments were conducted by a team of experienced, trained, and standardized psychologists using globally accepted tools with local adaptations. All the three studies had a clear statistical analysis plan and adjustment for relevant confounders was done in appropriate statistical models.

Limitations

Based on the review of literature, we identified several key risk factors for sub-optimal child development in LMIC settings. These risk factors were related to adverse birth

outcomes such as prematurity and small for gestational age, linear growth faltering, nutritional deficiencies such as iodine and iron deficiency, environmental toxins, maternal mental health, infections such as malaria and inadequate child stimulation including adverse form of child maltreatment such as violence and abuse. While addressing these risk factors, alone or in combination, may have significant advantages in terms of improving child development, we were limited by the feasibility within the context of the thesis.

There were some important limitations for each of the three studies included in this thesis. For the RCT that examined the effect of two milk-cereal mixes enriched with MMN, compared to no-supplementation, on neurodevelopment of children, the key limitation was the lack of blinding for the three study groups. In order to address this, blinding was ensured for the two supplementation groups by differential coded labelling known only to an independent statistician. The psychologists conducting assessments were blinded to the group allocation. However, there is a possibility that they are aware of the child supplementation status (whether supplemented or not) and this may have biased their assessment of child's development. The likelihood of behavioural modification(s) in intervention group mothers, such as those related to complementary feeding and care-seeking, due to higher frequency of home visits by the study team members, could not be ruled out. Such behavioural modifications could have affected infant care practices at home, thereby, influencing child development in either direction.

Data on compliance was collected by checking empty sachets of the supplement provided to the mother on a weekly basis. We acknowledge that empty sachets may not imply that the milk-cereal mix was consumed by the infant enrolled. In the absence of a direct and reliable method of reporting consumption such as directly observed feeding, it was challenging to ascertain differences in protein intake and utilisation between the groups. Further, the possibility of intra-household sharing of the supplements cannot be ruled out. Nonetheless, we made an attempt to minimize sharing by informing the families that the mix was meant only for young children and by providing biscuits/cookies for other children in the household.

For the study exploring the association between change in linear growth between early and late childhood (i.e., ages 12-36 months to 6-9 years) and neurodevelopment, the growth measurements were available only at two time points which limited our ability to conduct a more granular analysis based on the precise timings of growth improvement/faltering. We had used WISC and CVS for assessments which have been validated in Indian setting. However, the other tools such as NEPSY and BRIEF have not been validated yet. We used a combined WISC-IV^{INDIA} and CVS z-score based on converted z-scores for the three index scores in the WISC-IV^{INDIA} and the total CVS score. This was done as the WISC-IV^{INDIA} verbal comprehension tests required English language skills and CVS was available in Hindi with Indian norms. We did not have reliable data on gestational age, therefore we could not look at the differential effect of catch-up growth on cognitive outcomes based on premature, small for gestational age and term-appropriate for gestation age children.

The third study had examined the influence of linear growth and child stimulation at home on neurodevelopment among low-birth-weight infants. Consequently, the findings of this study have limited generalizability i.e., they could only be applicable to children born LBW and caution should be exerted when generalizing to high-income settings where the aetiology of LBW is different. In both the studies that used secondary data (study 2 and 3), the possibility of the results being affected by unmeasured confounding cannot be ruled out.

Ethical considerations

All the three studies followed the ethical principles laid down by the Declaration of Helsinki for medical research involving human subjects (148,149). Ethical approvals for the studies were taken from relevant ethics committees in India and Norway. Prior to collecting any data, written informed consents were obtained from mothers/primary caregivers of eligible infants and/or children.

CONCLUSION

Overall, the findings of the thesis emphasize that child neurodevelopment is influenced by a combination of interacting risk factors therefore, the approach of "one size fits all" may not yield desired improvements in early child development. We have shown that linear growth in the first 24 months of life is associated with concurrent and later neurodevelopment. Further, improvements in linear growth and/or reduction in stunting beyond the first 24 months is not associated with improvement in neurodevelopmental outcomes in later childhood. Our findings also indicate that the association between linear growth and neurodevelopment, particularly during infancy and in those born low birth weight, may be modified by the quality of child stimulation and nurturing care available. We found that with higher levels of stimulation and nurturance at home, the association between linear growth and neurodevelopmental scores was attenuated and a high-quality home environment could alleviate the risk of poor development scores in LBW infants with linear growth deficits. With respect to the nutritional supplementation during infancy, we found that supplementation with modest amount of protein and multiple micronutrients may lead to short term small improvements in motor function and infant temperament. On the contrary, there appears no advantage of supplementing with high protein.

FUTURE PERSPECTIVES

Based on our findings, we suggest that efforts to improve child neurodevelopment, including promotion of linear growth, should be initiated very early in childhood with optimal nurturing care as an integral component. Taking into account the findings from our RCT, we suggest cautious supplementation with high amounts of milk-based protein; however, supplementation with modest amounts of protein in early infancy may have some short-term beneficial effects on certain aspects of development.

Our findings lay emphasis on the need for a target-based approach wherein children that would benefit from a particular set of interventions are identified. Principles of identification may be based on relatively easy to measure indicators such as birth weight, child anthropometry (length, weight, mid-upper arm circumference) and whether the child is able to attain appropriate age-specific growth and development specific milestones. Longer follow up of infants and children is required to provide more insights on the effect of nutritional supplementation during early childhood on neurodevelopment and metabolic health later into childhood and adolescence.

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Milk–cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomised controlled trial in India

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Abstract

Inadequate protein intake and lack of micronutrients may affect neurodevelopment in infants. This randomised controlled trial was conducted to measure the effect of two milk–cereal mixes with modest and high amounts of protein and enriched with multiple micronutrients, given between 6 and 12 months, on cognitive, language, motor and behavioural scores at 12 and 24 months of age, compared with no-supplementation. The two supplements were also compared with each other. The study was conducted in urban Delhi, India, and the infants were randomised in a 1:1:1 ratio to the three study groups. At 12 and 24 months of age, 1134 and 1214 children were available, respectively. At 12 months of age, compared with no-supplement group, an increase in the motor scores (mean difference, MD 1·52, 95 % CI: 0·28, 2·75) and a decrease in the infant temperament scores (MD − 2·76, 95 % CI: −4·23, −1·29) in the modest-protein group was observed. Those in the high-protein group had lower socio-emotional scores (MD − 1·40, 95 % CI: −2·43, −0·37) and higher scores on Infant Temperament Scale (MD 2·05, 95 % CI: 0·62, 3·48) when compared with modest-protein group. At 24 months, no significant differences in any of the neurodevelopment scores between the three study groups was found. In conclusion, supplementation with modest amount of protein and multiple micronutrients may lead to short-term small improvements in motor function and infant temperament. There appears no advantage of supplementing with high protein, rather negative effects on infant behaviour were observed

Key words: **Neurodevelopment: Infancy: Milk protein: Nutritional supplementation: Randomised controlled trial: India**

About 250 million under-five children in low- and middle-income countries (LMIC) do not reach their full developmental potential[1]. Sub-Saharan Africa (43·8 %) followed by South Asia (37·7 %) are the leading contributors[1]. The brain growth occurs maximally in the first 2–3 years of postnatal life, particularly during infancy[2,3]. Adequate nutrition plays an important role in promoting healthy brain growth and development[4,5]. Complementary feeding is usually inadequate in low-resource populations in low- and middle-income countries. The concerns are both with the quantity and quality of complementary foods, and the infants often fail to achieve an adequate intake of key nutrients for optimal growth and development[6–9]. A review on the quality of complementary foods in low-resource settings documented that about 50–75 % of the total protein a child eats is from cereals and other plant sources[10]. Evidence suggests that in diets deriving over 50 % of protein from cereal sources, protein quality is relatively poor, thereby limiting protein utilisation, which in turn may adversely impact overall growth and development[9–11].

Proteins are specially required for brain development. They have a useful role to play in neurogenesis, neuronal migration and differentiation, synaptogenesis, oligodendrocyte myelination, neurotransmitter production and reuptake, and maintaining electrical efficiency[5,12,13]. Proteins obtained from dairy sources have been documented to increase the levels of insulin-like growth factor-1 which is a neurotrophic polypeptide playing a

Abbreviations: MD, mean difference.

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crucial role in growth, development and maturation of the central nervous system[14–16]. Supplementary Fig. 1 provides a conceptual framework through which supplementation with protein may promote neurodevelopment in children. Limited studies suggest an association of protein intakes in children with improvement in their neurodevelopment outcomes[17–19]. We currently do not fully understand the effects of supplementing with food that has higher amounts and improved quality of protein, that is, animal/milk source protein, to infants on their neurodevelopment. An effort to elucidate the usefulness of optimised nutritional interventions during the second half of infancy, that coincides with the period of complementary feeding, is required to guide the design of nutritional programmes for infants in low-middle-income settings. The present study aimed to test the effect of micronutrient-enriched milk–cereal-based supplements, differing in their protein content, provided to infants aged 6 months of age, for a period of 180 d, on neurodevelopmental outcomes at 12 months of age, when compared with no-supplementation. The intent was also to compare the two supplements with each other to understand whether increasing the amount and quality of proteins in the supplements led to a difference in neurodevelopmental outcomes. These infants were followed up without any supplementation in the period between 12 and 24 months, and their neurodevelopment was assessed again at 24 months of age. This was done to explore whether a nutritional intervention of short duration in early infancy can impact neurodevelopment in early childhood. The study is a part of a primary trial that assessed the impact of such nutritional supplementation during infancy on linear growth at 12 months of age[20]. In the primary trial, small improvement in length-for-age z scores (mean difference, MD 0·08), weight-for-age *z* scores (MD 0·12), weight-for-length *z* scores (MD 0·11) and mid-upper arm circumference *z* scores (MD 0·10) in the high-protein group was observed, when compared with no-supplement group.

Materials and methods

Study setting, design and participants

Details of the parent study have been published previously (CTRI/2018/04/012932)[20]. Infants enrolled in this parent trial were separately consented at 12 months for their neurodevelopmental assessments at 12 and 24 months and anthropometric assessments at 15, 18 and 24 months of age. The parent study was an individually randomised controlled efficacy trial conducted in low-resource settings in urban Delhi, India. Study subjects were infants aged 6 months (+29 d) who were breastfed. Infants not breastfed at the time of enrolment, those with documented illness requiring prolonged institutional management, with severe acute malnutrition (weight-for-height < −3 SD), with major congenital malformations and mother–infant dyads that were likely to move out of the study site within 6 months were excluded[20].

Screening and enrolment

A door-to-door survey was conducted to identify infants aged 6 months (+29 d). Those aged under 6 months were followed up periodically until they reached 6 months. The screening and enrolment team visited the family and explained the study to the mother and family members. If the infant was found eligible, consent for screening was obtained from the mother.

Randomisation, allocation and blinding

Eligible infants were randomised to either one of the two intervention groups or the control groups (allocation ratio of 1:1:1) through a web-based system[20]. A randomisation list with blocks of variable length (i.e. 3 and 6) was used. Complete blinding of the study intervention delivery team and participants was not possible due to the nature of the intervention, that is, no milk–cereal mix supplemented in the control, but supplements provided to infants in two intervention groups. However, blinding was ensured for the two intervention groups that differed in the amount and quality of milk protein supplemented[20]. Two different sets, each having thirteen unique English language alphabets, were allotted to the two infant cereal mixes. An offsite person (Statistician from WHO, Geneva, Switzerland) not associated directly with the trial prepared the list of alphabets and their scheme of allocation. The two milk–cereal mixes were identical in packaging, taste, consistency and colour. The outcome assessment team comprising of psychologists were blinded to the group allocation.

Study interventions

The details of the interventions, the nutritional composition of the milk–cereal mixes and the implementation strategy have been previously published in detail[20]. Infants in the control group received no milk–cereal mixes. Counselling was provided to mothers and family members by trained nutritionists on continued breast-feeding, optimal complementary feeding practices, infant care practices such as immunisation, early recognition and timely care-seeking for illness in all the three study groups. Infants were provided iron folic acid syrup (10 mg elemental iron and 100 mcg folic acid) in the three groups[21]. Infants in modest and high-protein groups received daily supplementation, for 180 d, with milk–cereal mix that provided about 125 kcal of energy, 30–45 % energy from fats and 80–100 % RDA of growth-relevant multiple micronutrients[20]. The difference in the supplement in these two groups was in the total amount of protein (modest group: 2·5 g protein, protein energy ratio of 8 %; high group: 5·6 g protein, protein energy ratio of 18 %) and absolute amount of protein from milk source (modest group: 30 % of the total protein from milk, i.e. 0·75 g; high group: 30 % of the total protein from milk, i.e. 1·68 g). The infant milk–cereal mix was designed in a way that it should provide about 50–60 % of the non-breast milk energy requirement. The cereal mixes were replenished on a weekly basis.

The intervention delivery team visited households to provide weekly supplies of milk–cereal sachets to mothers in both the intervention groups. During the weekly visits, this team gathered information on compliance by collecting packets of the mix and reinforced intake. The team collected information on the number of empty sachets and number of sachets with some of the mix remaining. As part of the study processes, the team collected information in their diaries on the consumed amount in the

collected sachets, i.e. completely consumed, not at all consumed, half to three-fourth or less than half of the content consumed. This information was used to identify subjects with low compliance, and they were then visited by the team supervisor to discuss barriers to optimal intake. Some measures taken to prevent intra-household sharing were that the milk–cereal mix was promoted for use for young children and not for older children or adults. Further, in order to prevent sharing, biscuits/cookies were provided for other children in the household.

Sample size and selection of participants

We considered a 0·25 SD MD (3·75 points, 1 SD = 15 points)[22] in cognitive, motor and language scores at 12 months between the modest-protein group and the no-supplement group and a 0·30 SD (4·5 points) difference between the high-protein group and the no-supplement group. With 90 % power, two-sided 5 % α level and 20 % attrition, 400 infants per group were required for the comparisons between the modest-protein and no-supplement group and 280 infants per group for comparisons between high-protein group and no-supplement group. We, therefore, aimed to include a total of about 1200 infants for the assessment of neurodevelopment outcomes. With a sample size of 400 infants each in modest-protein and high-protein groups, we were powered at 80 % to detect a difference of 2·5 points (0·17 SD)[22] in cognitive, motor and language scores between the two supplement groups. The 1200 infants were planned to be followed up for their neurodevelopment assessments at 24 months of age.

The children for neurodevelopment assessments were contacted in a consecutive manner, that is, as and when they completed their anthropometric and biochemical assessments in the primary trial at 12 months of age. The family members of these children were approached for their consent for participation in the neurodevelopment assessments at 12 and 24 months of age. For infants who could not be contacted at 12 months of age because the family members had temporarily moved out of the study area at the time of house visit or in those who had crossed the window period of +4 weeks at the time they were approached for inclusion in this study, the study team visited the house at the time of anthropometric assessments at 15 months of age and obtained written informed consent for neurodevelopment assessments at 24 months of age. Such children did not have their 12 months neurodevelopment assessments but were eligible for assessments at 24 months.

Outcomes and their ascertainment

The primary outcomes were cognitive, motor and language scores at 12 and 24 months of age. The secondary outcomes were socio-emotional scores at 12 and 24 months of age, infant temperament scores at 12 months of age, and mean internalising and externalising behaviour scores at 24 months of age. A window period of +4 weeks was considered for the assessments to be conducted. Details of the data collection have been presented previously[20]. A 24-h dietary recall at 12 and 24 months of age was done in a subsample of infants and children undergoing neurodevelopmental assessments by trained nutritionists. Data on morbidities were collected for the previous 2 weeks for visits done at 9, 12 and 24 months of age. Anthropometric assessments were conducted by trained and standardised workers at 15, 18 and 24 months of age.

For the neurodevelopmental outcomes, an independent team of trained and standardised psychologists conducted the assessments. This team was blinded to the group allocation. For the primary outcomes, Bayley Scales of Infant and Toddler Development (BSID), 3rd edition was used[22,23]. This is a comprehensive assessment tool of developmental functioning in infants and toddlers aged 1–42 months. The process of adaptation of BSID for use in the study setting has been previously described[24]. The inter-rater agreement for the standardisation exercises before the start of the study as well as during the conduct of the assessments was excellent (intraclass correlation: 0·94–0·99). Infant temperament was assessed using Infant Temperament Scale, which is a parent-reported measure containing forty-seven items that assess six dimensions (activity, positive emotionality, negative emotionality, sociability, attention and soothability). Higher scores on Infant Temperament Scale reflect difficult temperament[25]. The scale has been adapted for use in low-middle-income setting and has been used previously in one of our recent studies[24,25].

Behavioural problems were assessed using Child Behavior Checklist – preschool (CBCL). This is a caregiver-reported tool intended for children aged 18 months to 5 years[26]. It consists of 100 items, where the responses are recorded on a Likert scale. The responses are summed to provide a score for internalising and externalising behavioural problems. A total score from all questions is derived by adding up the internalising scores, externalising scores, scores pertaining to sleep problems and other problems. The raw scores are converted into t-scores, and increasing t-scores indicate the behavioural problems in a child. The tool has been used in previous research conducted in similar settings[24,25,27,28].

We also measured home environment and child stimulation by caregivers. Home environment at 12 months of child age was assessed using 'Pediatric Review of Children's Environmental Support and Stimulation (PROCESS)' questionnaire[29,30]. It consists of three components: a parent questionnaire, clinical observation and a toy checklist. Total scores are summed across the three sections, and higher scores reflect better stimulation and support to infants. For assessing home environment and stimulation at 24 months of age, we used the Home Observation for Measurement of the Environment (HOME) tool for infants and toddlers[31]. Both the PROCESS and HOME tools were used after adapting according to local cultural context, translating in local language (Hindi) and pre-testing for use.

Statistical analysis

All analyses were done using STATA version 16.0 (Stata-Corp LLC). We calculated the means (SD) or median (IQR, interquartile range) for continuous variables and proportions for categorical variables. Means (standard error, SE) of dietary intakes for energy, carbohydrates, protein and fats for children in each of the three groups were calculated using data from a single 24-h dietary recall at 12 and 24 months of age.

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The primary analysis included the comparison of neurodevelopment outcomes at 12 and 24 months of age between the three study groups and was based on the intention-to-treat principle. Effect sizes (difference in means and 95 % CI) for the continuous outcomes were calculated using generalised linear models of the Gaussian family with an identity-link function. The primary analysis was unadjusted as there were no significant differences in the baseline characteristics among children in the three groups. Additionally, we also conducted an adjusted analysis after including variables in the models that have been shown to influence neurodevelopment outcomes, based on previously published studies[1,32–34]. We used generalised estimating equation models when the outcomes were measured more than once for the children. We used generalised estimating equation models of the Gaussian family with an identity-link function, an autoregressive covariance–variance matrix that factored in time and calculated robust standard errors. Although not an *a priori* decision, we conducted subgroup analysis with infants who were stunted (length-for-age z-scores, LAZ < −2) at the time of enrolment in the study in order to explore whether there were any differential effects of supplementation on neurodevelopment outcomes at 12 and 24 months of age in these high-risk infants. For this subgroup analysis, we adjusted for variables that were selected based on prior literature and biological plausibility to influence child development outcomes. This adjustment was done as the original randomisation was not preserved when utilising this subgroup.

Results

The primary trial assessed the impact of milk–cereal mix supplementation on linear growth at 12 months in a total of 1548 infants[20]. From these, 1134 infants were assessed for their neurodevelopment at 12 months (high protein, *n* 372; modest protein, *n* 388; no supplement, *n* 374) and 1214 children (high protein, *n* 404; modest protein, *n* 408; no supplement, *n* 402) at 24 months of age (Fig. 1). The reasons for non-participation were mainly related to families moving out of the study area, refusing to participate, or that the child had crossed the window period of +4 weeks at the time of contact (Fig. 1). Findings on compliance to the milk–cereal mix and iron folic acid (IFA) among the three groups have been presented previously[20]. The proportion of infants consuming milk–cereal mix on > 75 % of days of the 180 d supplementation period was > 80 % for both modest-protein and high-protein group. The proportion of infants who consumed iron folic acid for > 75 % of days was about 70 % for the three groups. The baseline characteristics (i.e. at the time of enrolment in the primary trial) of the children assessed for their neurodevelopment at 12 and 24 months of age were statistically similar across the three groups (Table 1). The mean (SD) LAZ and weight-for-age z scores (WAZ) at 24 months of age were statistically similar among the three groups (LAZ: −1·36 (0·99), −1·41 (1·01), −1·43 (1·05) and WAZ: −1·37 (0·98), −1·40 (1·07), −1·42 (0·99) for the high-protein, moderate-protein and no-supplement group, respectively). The mean (SD) PROCESS score at 12 months (125·0 (11·9); 125·5 (12·7); 125·0 (12·8)) and HOME score at 24 months (39·1 (5·5); 38·9 (4·9); 39·0 (5·3)) were statistically similar among the high-protein, modest-protein and no-supplement group, respectively.

The findings of the analysis for the effect of supplementation on neurodevelopment outcomes at 12 months of age have been presented in Table 2. Compared with no-supplement group, there was an increase in the motor scores in the modest-protein group (MD 1·52, 95 % CI: 0·28, 2·75) but not in high-protein group (Table 2). No difference in motor scores was found for comparison between modest- and high-protein groups. There were no significant differences in the cognitive and language scores for any of the three comparisons, i.e. modest-protein *v.* no-supplement group, high-protein *v.* no-supplement group and modest-protein *v.* high-protein group. Those in high-protein group had lower socio-emotional scores when compared with modest-protein group (MD − 1·40, 95 % CI: −2·43, −0·37) (Table 2). Analysis of Infant Temperament Scale scores revealed lower scores for modest-protein group compared with no-supplement group (MD − 2·76, 95 % CI: −4·23, −1·29) and higher scores for high-protein group compared with modest-protein group (MD 2·05, 95 % CI: 0·62, 3·48) (Table 2). Similar findings were observed in the adjusted analysis (online Supplementary Table 1)

At 24 months of age, there were no significant differences in the cognitive, motor, language and socio-emotional scores as well as in the scores for internalising behaviour, externalising behaviour and total problem for any of the three comparisons (Table 3; online Supplementary Table 2). In the generalised estimating equation analysis, compared with no-supplement group, only children in the modest-protein group had some improvement in their motor scores over the 12 months follow-up period (i.e. from 12 to 24 months of age) (MD 0·98, 95 % CI: 0·06, 1·91) (Table 4). There were no significant differences in the changes in cognitive and language scores across the 12 months follow-up period for modest- and high-protein groups, when compared with no-supplement group (Table 4). No significant differences in cognitive, motor and language scores were found for generalised estimating equation-based comparisons between modest- and high-protein groups.

The proportion of children with morbidities was similar across the three groups at 9, 12 and 24 months of age (online Supplementary Tables 3 and 4). Supplementary Table 5 presents the findings from the dietary recalls at 12 and 24 months of age from a small subsample of children. At 12 months, the total energy, fat and carbohydrate consumption by infants was statistically similar in the three groups. The amount of protein consumed significantly differed among the groups, with highest intake in the high-protein group. Overall, the total energy consumed was lower, whereas the total amount of protein consumed was higher than the RDA among infants in all the three groups. At 24 months, the total energy, fat and protein consumption by children was statistically similar in the three groups. The amount of carbohydrate consumed differed among the groups, with highest intake in the no-supplement group and lowest in high-protein group. Even at 24 months of age, the total energy consumed was lower and the total amount of protein consumed was higher than the RDA among infants in all the three groups.

The subgroup analysis among infants stunted at the time of enrolment in the trial suggested a significant beneficial effect

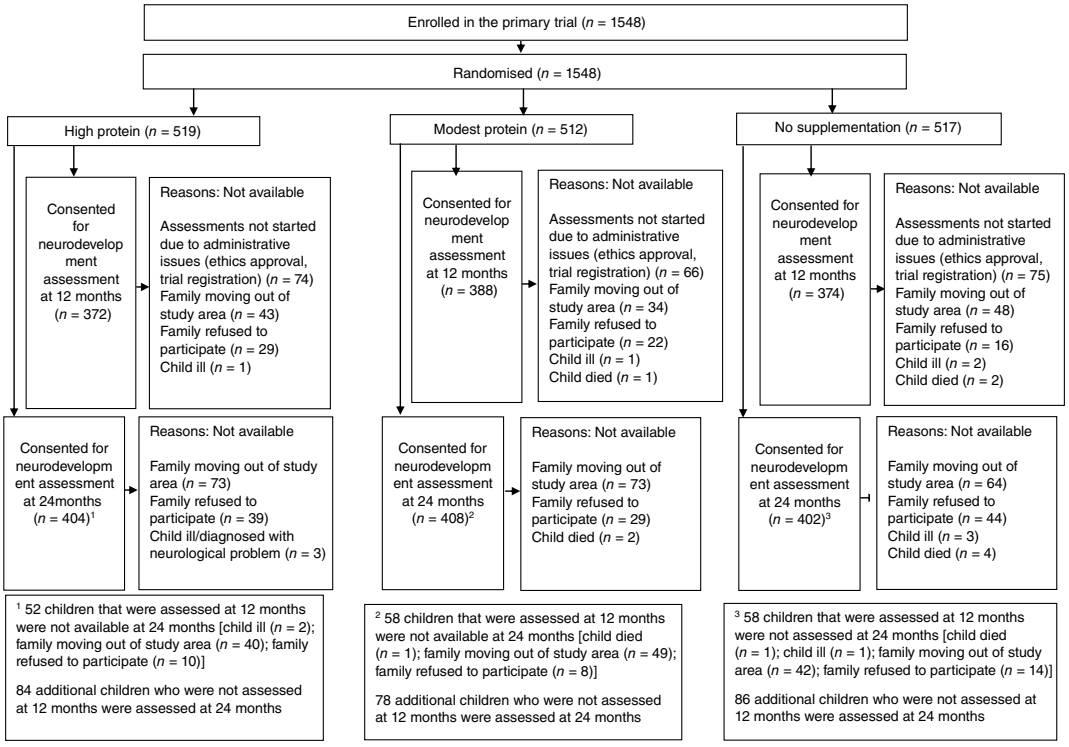

Fig. 1. Trial profile. For 12 months of neurodevelopment assessment, some infants had crossed the window period of +4 weeks at the time they were approached for consenting. For these children, the study team visited the house at the time of anthropometric assessments at 15 months of age and obtained written informed consent for neurodevelopment assessments at 24 months of age.

in modest-protein group, compared with no-supplementation group, on cognitive, motor and language scores at 12 months of age (online Supplementary Table 6). Compared with infants in the modest-protein group, those in the high-protein group had significantly lower cognitive, language and socio-emotional scores at 12 months of age. No differences were observed in cognitive, motor, language and socio-emotional scores among the three groups at 24 months of age (online Supplementary Table 6).

Discussion

The current study was conducted to measure the effect of supplementing infants, for a period of 180 d, with micronutrient-enriched milk–cereal mixes containing varying amounts of protein (modest and high) on their neurodevelopment at 12 and 24 months of age. We found that compared with no supplementation, those receiving modest amount of protein had better motor scores (about 0·17 SD, considering 1 SD of 8·9 points in no-supplementation group) and less difficult temperament at 12 months of age. At this time point, the cognitive, motor, language and socio-emotional scores were similar between the high-protein and no-supplement group. The socio-emotional scores were lower and infant temperament scores higher, reflecting difficult temperament, for infants in the high-protein group compared with the modest-protein group. At 24 months of age, there was no effect of the intervention on any of the outcomes.

Existing direct evidence on the effect of protein supplementation during infancy and early childhood on neurodevelopment is limited and makes it difficult to arrive at a consensus. In most of the available studies, there is a lack of clear specification of the source of animal protein being investigated (i.e. milk or meat based)[35]. Further, the age range of children being studied is diverse and limits comparability. In a trial in Guatemala, pregnant women and their children up to the age of 7 years were supplemented with a milk-based high protein and energy drink with micronutrients (11·5 gm protein: 163 kcal) or a no-protein, low-energy drink with micronutrients (59 kcal)[19]. Children who received the high protein and energy drink had higher cognitive scores at 4–5 years of age, higher scores on tests of numeracy, vocabulary, and reading achievement at 11–18 years of age as well as improved reading and intelligence quotient (IQ) scores in adulthood[19,36]. In another study among Indonesian children aged 6–20 months supplemented (for 3 months) with snacks

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Table 1. Baseline characteristics of the children assessed and their families, by the study groups

	Children assessed at 12 months						Children assessed at 24 months					
	Modest-protein group (*n* 388)		High-protein group (*n* 372)		No-supplement group (*n* 374)		Modest-protein group (*n* 408)		High-protein group (*n* 404)		No-supplement group (*n* 402)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Infant characteristics												
Proportion of male infants	205	52·8	178	47·9	198	52·9	200	49·0	189	46·8	209	52·0
LAZ scores*												
Mean	–1·21		–1·15		–1·20		–1·19		–1·12		–1·21	
SD	1·12		1·92		1·02		1·0		1·04		0·99	
Stunted (< –2 LAZ)	89	22·9	76	20·4	78	20·9	92	22·6	81	20·1	82	20·4
WLZ scores*												
Mean	–0·44		–0·44		–0·48		–0·43		–0·37		–0·49	
SD	1·02		1·06		1·03		1·02		1·09		1·01	
Wasted (< –2 WLZ)	23	5·9	33	8·9	24	6·4	23	5·6	29	7·2	21	5·2
WAZ scores*												
Mean	–1·13		–1·10		–1·15		–1·12		–1·02		–1·17	
SD	1·05		1·14		1·09		1·05		1·08		1·03	
Underweight (< –2 WAZ)	75	19·3	68	18·3	81	21·7	80	19·6	66	16·3	88	21·9
Birth order												
Mean	2·18		2.20		2·15		2·14		2·16		2·15	
SD	1·13		1·32		1·31		1·13		1·22		1·22	
Socio-demographic characteristics												
Wealth quintile												
Poorest	70	18·0	69	18·6	62	16·6	73	17·9	70	17·3	74	18·4
Very poor	77	19·9	68	18·3	83	22·2	75	18·4	72	17·8	88	21·9
Poor	87	22·4	72	19·3	75	20·1	95	23·3	77	19·1	80	19·9
Less poor	67	17·3	79	21·2	82	21·9	76	18·6	95	23·5	90	22·4
Least poor	87	22·4	84	22·6	72	19·2	89	21·8	90	22·3	70	17·4
Maternal characteristics												
Age (years)												
Mean	25·2		25·4		25·3		24·9		25·4		25·2	
SD	4·1		3·9		4·2		3·9		4·0		4·1	
Duration of schooling (in years)												
Median	8		8		8		8		8		8	
IQR	5–10		3·5–10		4–10		4·5–10		4·5–10		3–10	
Never been to school	75	19·3	81	21·8	74	19·8	81	19·9	88	21·8	90	22·4
Homemakers	364	93·8	350	94·1	352	94·1	383	93·9	379	93·8	379	94·3
Paternal characteristics												
Age (in years)												
Mean	28·8		29·0		28·9		28·5		29·1		28·8	
SD	4·8		4·5		4·8		4·6		4·7		4·6	
Duration of schooling (in years)												
Median	8		8		9		8		8		8·5	
IQR	5–10		5–10		6–12		5–10		5–10		5–10	
Unemployed	5	1·3	11	3·0	8	2·1	6	1·5	11	2·7	8	2·0

LAZ, length-for-age z scores; WLZ, weight-for-length z-scores; WAZ, weight-for-age z-scores; IQR, interquartile range.
Values are mean and standard deviation unless reported otherwise.
* Calculated using WHO standards.

having protein and energy (400 Kcal; 5 g protein/d), a positive effect on motor scores was observed[37]. We also observed a significant effect of short-term supplementation with modest amounts of protein on motor scores at 12 months of age. Further, when these Indonesian children were 8–9 years old, the study found a beneficial effect on tests of working memory[38]. Rask-Nissilä *et al.* through a sample of 496 Finnish children found that protein intake was associated with improved language scores at the age of 5 years in boys[18].

There are many plausible explanations for why we did not observe significant effects of protein supplementation on neurodevelopment. One of the reasons might be the similarity in the amounts of total protein intake and protein energy ratio between the children in the three study groups. Seemingly adequate protein intake in the control group may be responsible for lack of any additional benefit of moderate or high protein intake. The data from the 24-h dietary recall in a small subsample of children may appear to support this argument. However, there are limitations in terms of extrapolation of the findings of this recall to the entire sample of children studied. We found some positive effect of modest protein supplementation, compared with no-supplement group, on motor scores and infant temperament. This small overall effect might be due to a beneficial effect in subgroups consisting of few participants who would have benefitted from additional protein. Our intervention was focused during second half of infancy, whereas most of the studies that have shown an impact have also covered the period of pregnancy and lactation[13,19,39]. The duration of supplementation was also relatively

Table 2. Effect of infant nutritional supplementation on neurodevelopment outcomes at 12 months of age

	Modest-protein group (*n* 388)		High-protein group (*n* 372)		No-supplement group (*n* 374)		Mean difference (95 % CI)					
							Modest-protein group *v.* no-supplement group (Ref)		High-protein group *v.* no-supplement group (Ref)		High-protein group *v.* modest-protein group (Ref)	
	Mean	SD	Mean	SD	Mean	SD	Mean difference	95 % CI	Mean difference	95 % CI	Mean difference	95 % CI
BSID composite scores												
Cognitive	105·3	10·0	105·1	10·0	104·2	11·3	1·09	–0·44, 2·61	0·91	–0·63, 2·45	–0·18	–1·60, 1·25
Motor	95·7	8·4	94·9	9·1	94·2	8·9	1·52	0·28, 2·75*	0·77	–0·53, 2·06	–0·75	–1·99, 0·49
Language	95·6	8·4	94·8	8·6	94·6	8·9	1·02	–0·22, 2·26	0·22	–1·04, 1·49	–0·80	–2·01, 0·42
Socio-emotional	98	7·5	96·6	7·0	97·1	7·9	0·88	–0·22, 1·97	–0·53	–1·60, 0·55	–1·40	–2·43, –0·37†
Infant temperament												
Total infant temperament scores	109·2	9·7	111·2	10·4	111·9	10·9	–2·76	–4·23, –1·29†	–0·71	–2·24, 0·82	2·05	0·62, 3·48†

BSID, Bayley Scales of Infant and Toddler Development; CI, confidence interval.
* Statistically significant at $P < 0·05$.
† Statistically significant at $P < 0·01$.

Table 3. Effect of infant nutritional supplementation on neurodevelopment outcomes at 24 months of age

	Modest-protein group (*n* 408)		High-protein group (*n* 404)		No-supplement group (*n* 402)		Mean difference (95 % CI)					
							Modest-protein group *v.* no-supplement group (Ref)		High-protein group *v.* no-supplement group (Ref)		High-protein group *v.* Modest-protein group (Ref)	
	Mean	SD	Mean	SD	Mean	SD	Mean difference	95 % CI	Mean difference	95 % CI	Mean difference	95 % CI
BSID composite scores												
Cognitive	92·1	7·4	92·1	6·8	91·7	6·9	0·38	–0·60, 1·36	0·38	–0·57, 1·32	0·00	–0·98, 0·97
Motor	94·4	8·1	94·3	8·3	94·0	8·3	0·35	–0·78, 1·48	0·34	–0·81, 1·49	–0·01	–1·14, 1·11
Language	88·9	9·8	89·8	9·6	89·8	9·5	–0·92	–2·25, 0·40	–0·08	–1·39, 1·24	0·84	–0·48, 2·18
Socio-emotional	104·9	17·1	105·6	16·2	105·1	16·9	–0·14	–2·49, 2·22	0·43	–1·86, 2·72	0·57	–1·73, 2·86
Child behaviour checklist scores												
Internalising behaviour t-scores	36·6	7·2	36·2	7·0	35·8	6·6	0·80	–0·15, 1·75	0·40	–0·54, 1·34	–0·40	–0·58, 1·38
Externalising behaviour t-scores	44·7	10·4	45·2	9·8	45·5	9·6	–0·82	–2·20, 0·56	–0·40	–1·75, 0·94	0·42	–0·97, 1·82
Total problem t-scores	39·6	8·5	39·4	7·5	39·3	7·4	0·24	–0·86, 1·34	0·03	–0·99, 1·06	–0·21	–1·31, 0·90

BSID, Bayley Scales of Infant and Toddler Development; CI, confidence interval.

Table 4. Effect of supplementation with milk–cereal mix during infancy on cognitive, motor and language scores between 12 and 24 months of age using a GEE model

BSID composite scores	Modest-protein group *v.* no-supplement group (Ref)		High-protein group *v.* no-supplement group (Ref)		High-protein group *v.* modest-protein group (Ref)	
	Mean difference	95 % CI	Mean difference	95 % CI	Mean difference	95 % CI
Cognitive	0·79	–0·23, 1·80	0·61	–0·40, 1·61	–0·18	–1·17, 0·82
Motor	0·98	0·06, 1·91*	0·63	–0·34, 1·59	–0·35	–1·29, 0·58
Language	0·10	–0·95, 1·15	0·12	–0·94, 1·17	0·01	–1·03, 1·04

GEE, generalised estimating equation; BSID, Bayley Scales of Infant and Toddler Development.
Values are mean differences with 95 % CI, adjusted for time.
* Statistically significant at $P < 0·05$.

short, that is, 180 d and did not cover the critical period of 24 months entirely. We assessed neurodevelopment at 12 and 24 months of age, whereas most studies that documented an improvement conducted assessments in late childhood. It is well known that brain development tends to be more stable as the age increases, and therefore, any significant effect of an intervention can be reliably detected at later ages[40,41]. Another important aspect to consider is that child neurodevelopment is affected by multiple factors, with nutrition being one of them. Therefore, if the intent is to improve neurodevelopment outcome, investment is needed not only in nutrition but also in other aspects of nurturing care, especially responsive care and learning opportunities.

Similar to the present study, a recent systematic review and individual participant data meta-analysis (including data from about 30 000 children from thirteen RCT) found a modest improvement in motor, language and socio-emotional scores in children, aged 6–24 months, receiving small quantity lipid-based supplement[42]. The nutritional composition of small quantity lipid-based supplement was similar to the milk–cereal mix provided to infants in the modest-protein group in our study. Further, the review found an enhanced effect of supplementation in populations with high burden of stunted children[42]. In the present study, we observed that in the modest-protein group, infants stunted at the time of enrolment had significant improvements in cognitive, motor, language and socio-emotional scores at 12 months of age. Our study also found that supplementation with high protein was not favourably associated with certain aspects of child development. Some studies among high-risk infants observed an association between high-protein supplementation in the very early half of infancy and neurodevelopment impairment at about 24 months of age[43,44]. However, it still needs to be tested conclusively whether such an association truly exits and if so, the potential underlying mechanisms need to be identified.

Another possible disadvantage of providing infants with high-protein supplements is the likely increase in the risk of adverse metabolic health, as documented in studies from large cohorts[45,46]. A recent review found that children under the age of 2 years from affluent countries often have protein adequacy, and some also have protein consumption in excess of the physiological requirement[47]. The authors shared concerns about excess protein and its relation to subsequent development of overweight and obesity[47]. It has been suggested that protein energy ratio of 14 % in 12 to 24 months old children should be considered the maximum acceptable level[48]. In our study, firstly, the children were from low-resource settings with inadequate access of quality complementary foods and with a high likelihood of gut enteropathy, thereby negatively affecting protein absorption and increasing the demand. Secondly, based on the data on 24-h dietary recall, the protein consumption among the study children did not exceed the 14 % threshold. Nonetheless, we share the concern that one should be cautious while supplementing young children with high-protein diets.

The strength of our study lies in it being a randomised controlled trial done in a community setting. The study achieved high compliance to the supplementation, and the data collection was done by a highly trained team. The neurodevelopment assessments were done in a large sample of infants and children by a team of experienced psychologists. Some limitations included the lack of blinding for the three study groups. However, blinding was ensured for the two supplementation groups by differential coded labelling known only to an independent statistician. At 24 months of age, the behavioural outcomes assessed using CBCL were intended to be presented as proportions, that is, those with internalising and externalising behaviour across the three study groups. However, the numbers of children with clinically significant behavioural problems were very small for a meaningful analysis based on proportions. Another limitation might be in the way we collected data on compliance to milk–cereal mix supplement, that is, by checking empty sachets of the supplement. Empty sachets may not mean that the milk–cereal mix was consumed by the infant enrolled in our study. In the absence of a direct and reliable method of reporting consumption such as directly observed feeding, it may be challenging to ascertain differences in protein intake and utilisation between the groups. We did attempt to minimise sharing by informing the families that the mix was meant only for young children and by providing biscuits/cookies for other children in the household. In about 30 % of the families included in the study, the studied child was of first birth order. This might have reduced the proportion of families in which sharing occurred. However, in spite of these measures, there still remains a possibility of sharing. An additional limitation is that we conducted 24-h dietary recall in a small proportion of infants and children (about 10 % of the total sample) due to limited resources. It may have enhanced our understanding of the findings obtained if a larger subsample of children were assessed for their dietary intakes. Caution

should be exercised while drawing interpretations based on data from such a small sample.

Conclusion

In conclusion, the findings suggest some benefit of short-term supplementation (i.e. 180 d) during infancy with milk–cereal mix containing modest amount of protein and multiple micronutrients on the motor scores and infant temperament soon after supplementation ceased, that is, at 12 months of age, compared with no supplementation. These effects seem to be more pronounced among stunted infants. However, these benefits were not measurable 12 months later, that is, at 24 months of age. The study found no advantage of supplementing infants with milk–cereal mix having high protein, rather a low socio-emotional scores and difficult temperament at 12 months of age was observed. The findings are relevant from the policy perspective as increasing the amount of protein in the supplement increases the cost and has no added advantage. Longer follow-up of infants and children may provide more insights on the effect of nutritional supplementation on neurodevelopment later into childhood and adolescence.

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S. T., N. B., R. P. U. and R. B. designed the research; S. T., R. P. U., N. B. conducted the research; T. A. S., M. H., B. K. and R. B. provided technical inputs in study implementation and conduct of neurodevelopmental assessments; R. P. U, S. T., T. A. S. and M. H. analysed the data or performed statistical analysis; R. P. U., S. T., T. A. S. and M. H. prepared the manuscript. All the authors were responsible for the final content of this manuscript.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the ethics committee of the Centre for Health Research and Development, Society for Applied Studies, India (SAS/ERC/IMPRINT-FU/2019) and Regional committees for medical and health research ethics (REK), Norway (REK 2019/554). Written informed consent was obtained from the caregivers of eligible children before enrolment in the study, that is, at 12 months of age. There were infants who could not be contacted at the end of infancy. For these children, the study team visited the house at the time of anthropometric assessments at 15 months of age and obtained written informed consent for neurodevelopment assessments at 24 months of age. The study is registered on Clinical Trials Registry-India (CTRI/2019/03/018238) (http://ctri.nic.in/Clinicaltrials/login.php).

The authors report no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522003944

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Linear Growth between Early and Late Childhood and Cognitive Outcomes at 6-9 Years of Age

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Objectives To assess the extent to which linear growth beyond the early years of life determines later cognitive development.

Study design We revisited children from New Delhi, India, who had participated in a randomized controlled trial 6 years before and assessed neurodevelopment using standardized and validated psychometric tools (Wechsler Intelligence Scale for Children, 4th edition; Crichton Vocabulary Scales; and Neuropsychological test battery). The associations of change in height for age z scores between early (12-36 months) and late (6-9 years) childhood with cognitive outcomes at 6-9 years of age were explored using linear regression models, after adjustment for appropriate confounders.

Results Out of the 1000 North Indian children who were enrolled in the original study, 791 consented to participate in this follow-up. Height for age z scores in the first 2 years of life was significantly associated with both the Wechsler Intelligence Scale for Children-Crichton Vocabulary Scales (standardized β coefficient [β], 0.15; 95% CI, 0.08-0.23), and the Neuropsychological test battery-II z-score (β, 0.09; 95% CI, 0.03-0.18) at 6-9 years of age. There were no significant associations between change in height for age z scores between early and later childhood and Wechsler Intelligence Scale for Children-Crichton Vocabulary Scales (β, −0.03; 95% CI, −0.11 to 0.04) or Neuropsychological test battery-II z-scores (β, −0.04; 95% CI, −0.12 to 0.06).

Conclusions Linear growth between early and late childhood is not associated with later cognitive outcomes. Our findings support the current practice of investing public health efforts to accelerate linear growth in the first 2-3 years of life. *(J Pediatr 2020;225:214-21)*.

Brain development is substantial in the period from late gestation until the first 2-3 years of life.[1,2] Nutritional and other environmental insults during this period places the child at risk of linear growth deficits and subsequent long-lasting adverse effects on cognitive development.[1-3] Stunted growth is linked to delayed neurodevelopment and poor academic performance and improving linear growth in the first 2 years of life is associated with better developmental outcomes.[4-7] A meta-analysis of 68 studies from 29 low- and middle-income countries showed that each unit increase in height-for-age z-score (HAZ) for children ≤2 years of age was associated with a 0.22-SD increase in cognition at 5-11 years of age.[4] In children >2 years of age, the effect was less pronounced, and each unit increase in HAZ was associated with an increase of only 0.09-SD for the cognitive score.[4] It is worthwhile to note that, in this meta-analysis, the ability to adjust for important confounders such as socioeconomic status and child stimulation was limited. It is thought that growth failure and related cognitive deficits are difficult to reverse after the initial 2-3 years of age and, therefore, much of the resources are directed toward improving growth during this period.[8,9] It is important to explore if there is still an opportunity beyond this period when investments in improving linear growth can yield better results in terms of cognitive performance.

Recent studies suggest that a substantial recovery from early growth failure can take place.[10-16] However, it is not decisively understood if these improvements in growth are associated with improvements in cognitive capacities. Studies have assessed the effect of recovery from stunting on cognitive achievement in children and the evidence has been mixed.[10,11,13,14,16] These studies adjusted for socioeconomic variables, but did not take into account the child stimulation practices that might have distorted the direct effect of the linear growth improvement on cognitive abilities.[17,18] Current evidence, therefore, does not provide reliable guidance on the magnitude of improvement in developmental outcomes that could be expected as a result of

CVS	Crichton Vocabulary Scales
HAZ	Height-for-age z-scores
NEPSY-II	Neuropsychological test battery, 2nd edition
WISC-IV^{INDIA}	Wechsler Intelligence Scale for Children, 4th edition (India)

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accelerated growth after the first 2-3 years of age.[19] We conducted the current analysis to understand whether improvements in linear growth and/or change in stunting status between early and late childhood can lead to improved cognitive outcomes at ages 6-9 years, after adjustment for sociodemographic and child stimulation variables.

Methods

The current analyses use follow-up data from children who had previously participated in a randomized double-blind placebo-controlled trial on the effect of vitamin B_{12} and/or folic acid supplementation on childhood infections and growth in New Delhi, India.[20] The primary trial had a sample size of 1000 children aged 6-30 months at enrolment. Children were recruited at age 6-30 months from low to middle socioeconomic class families living in New Delhi and randomly assigned to receive placebo, vitamin B_{12}, folic acid, or vitamin B_{12} and folic acid supplements for a period of 6 months.[20] The intervention was a lipid-based nutritional supplement prepared by Nutriset, Ltd (Malaunay, France). Children were supplemented with 1 spoon (5 g) if they were 6-11 months of age and 2 spoons (10 g) if they were ≥12 months of age. Each 10 g of the supplement (dose for children aged ≥12) contained 54.1 kcal total energy, 0.7 g of protein, and 3.3 g of fat. For the groups that were assigned to receive B vitamins, the supplement also contained 1.8 μg of vitamin B_{12} or 150 mg of folic acid or both, constituting 2 recommended daily allowances.[20] In the follow-up study, an attempt was made to contact all the children in the primary trial. The study investigators were able to contact 798 children, and 791 consented to participate. The follow-up study aimed to examine the long-term effects of the 6-month supplementation of vitamin B_{12} and/or folic acid in early childhood on cognition at age 6-9 years.[21,22] The primary trial (CTRI/2010/091/001090) as well as the follow-up study (CTRI/2016/11/007494) were registered at Clinical Trials Registry-India (CTRI). The follow-up study obtained approval from the ethics committee of Society for Applied Studies (India) and from the Norwegian Regional Committee for Medical and Health Research Ethics (REK WEST).

Exposure and Outcomes

In the follow-up study, information was collected on socioeconomic status and child stimulation at home. The wealth of the family was determined by a wealth index created through a principal component analysis based on household assets. In the primary trial, trained field supervisors measured weight and length at the time of enrollment (ie, child age range of 6-30 months) and after 6 months of supplementation (ie, at age range of 12-36 months). Height, using a Seca 213 scale and reading to the nearest of 0.1cm; and weight, using Digitron scales to the nearest of 50 g, were also measured in the follow-up study (ie, at age range of 6-9 years) by trained and standardized study team members.

The cognitive assessments were conducted at the study clinic by trained psychologists. Ten percent of all assessments were double scored, attaining a kappa coefficient of agreement of >96%. Age appropriate psychometric assessment tools were used. Wechsler Intelligence Scale for Children 4th edition (India) (WISC-IV^{INDIA}) was used to assess general intellectual ability (IQ). This version has Indian norms and is validated for the Indian population.[23] Seven subtests were conducted, and their scores were summed up to 3 index scores: the perceptual reasoning (block design, picture concept, matrix reasoning), processing speed (symbol search, letter-number sequences), and working memory (digit span, coding). Because verbal comprehension tests in the WISC-IV^{INDIA} require English language skills, we substituted this component with Crichton Vocabulary Scales (CVS) to assess verbal skills.[24] The CVS has been translated to Hindi and has Indian norms providing a standard total score. We also included seven age-appropriate subtests from the Neuropsychological test battery, 2nd edition (NEPSY-II): inhibition, design fluency, word generation, visuomotor precision, manual motor sequences, affect recognition, and geometric puzzles.[25]

Statistical Analyses

Mean ± SD or median (IQR) were calculated for continuous variables and proportions for categorical variables. HAZ were calculated based on the World Health Organization Child Growth Standards.[26] Scores on the cognitive tests were calculated based on the available norms. An IQ can be calculated from the four index scores in WISC-IV^{INDIA}. Owing to the lack of the verbal comprehension index score, we calculated a combined WISC-IV^{INDIA} and CVS z-score based on converted z-scores for the 3 index scores in the WISC-IV^{INDIA} (the perceptual reasoning, processing speed, and working memory) and the total CVS score. We also calculated a combined NEPSY-II z-score based on converted z-scores in seven subtests.

For the analyses in the present study, we define "baseline" to denote measurements at the end of the primary trial (ie, at ages 12-36 months). To understand the association between the baseline HAZ score and cognitive scores at follow-up (ie, at ages 6-9 years), we performed a multivariable linear regression. We performed a purposive selection of covariates (socioeconomic, child characteristics and stimulation variables) for adjustment in the models based on the principles suggested by Hosmer and Lemeshow.[27,28] First, a univariate analysis was run with baseline HAZ score as the exposure and cognitive test scores as the outcome (model 1) and the resulting β-coefficient was noted. Thereafter, each of the covariates was added in the model, one by one, and the change in β-coefficient was noted. To improve the chances of retaining meaningful confounders, all covariates that brought ≥15% change in the β-coefficient were included in the multivariable model (model 2).[28] We estimated the interaction between baseline HAZ and age at baseline (categorized as ≤24 months and >24 months of age) for the neurodevelopmental outcomes. We conducted subgroup analyses with

children aged ≤24 months of age (model 3) and with children aged >24 months (model 4) to test whether HAZ scores in these subgroup of children are differentially associated with later neurodevelopment.

Stunting was defined as a HAZ of <−2, based on the standard World Health Organization definition.[26] We created four categories of change in stunting status (ie, persistently stunted—stunted both at baseline and at follow-up, considered the reference), never stunted (not stunted at baseline and follow-up), recovered (stunted at baseline and not stunted at follow-up), and faltered (not stunted at baseline and stunted at follow-up). Distribution of sociodemographics, child characteristics, and stimulation variables were presented across the four categories of change in stunting status. Multivariable linear regression models were developed with change in stunting status as the exposure and cognitive test scores as the outcome. As described elsewhere in this article, we performed purposive selection of covariates for adjustment in the model. A univariate analysis was run with change in stunting status as the exposure and cognitive test scores as the outcome (model 1). All those covariates that brought a ≥15% change in the coefficient were included in the multivariable model (model 2).[28] We also explored the interaction between change in stunting status and baseline HAZ score. In the absence of a significant interaction, a third model was created where adjustment for baseline HAZ scores was also done (model 3). We performed similar analyses for change in HAZ scores (from baseline to follow-up) as the exposure and cognitive test scores as the outcome. We created stunting categories at baseline (ie, stunted and nonstunted among children aged 12-36 months) and ran a stratified analysis to explore the association of change in HAZ with cognitive score within each stratum. We performed generalized additive model analysis to generate perspective plots to visually present the relationship between baseline HAZ score, change in HAZ score and the cognitive z-scores.[29]

Results

Of the 1000 children enrolled in the primary trial, 791 consented to participate in the follow-up study. Data on HAZ at both time points ie, at baseline and at follow-up were available for 773 children. The mean ± SD follow-up period was 5.95 ± 0.24 years and age of children at the time of follow-up assessments was 7.83 ± 0.65 years (Table I). The mean ± SDHAZ at baseline and at follow-up was −1.79 ± 1.1 and −1.02 ± 0.98, respectively. Among the study subjects, 397 (51.4%) were males and majority belonged to Hindu families (83.2%). The characteristics of the children have been presented in Table I.

Table I. Baseline characteristics of the study children (n = 773)

Variables	Total study population (n = 773)
Sociodemographic characteristics	
Annual family income (in USD)	2200 (1574-3930)
Religion	
Hindu	643 (83.2)
Muslim	111 (14.3)
Others (Jain/Sikh/Christian)	19 (2.5)
Social class*	
Scheduled caste/scheduled tribe	391 (50.6)
Other backward class	148 (19.1)
General class	234 (30.3)
Mother's age (in y)	31.5 ± 4.8
Mother's duration of schooling (in y)	7 (0-10)
Mother illiterate	206 (26.6)
Mother does not work outside home†	624 (82.1)
Father's duration of schooling (in y)	10 (7-12)
Father unemployed‡	30 (3.9)
Nuclear family	448 (58.0)
Number of living children in the family	
1	46 (6.0)
2-3	549 (71.0)
≥4	178 (23.0)
Child characteristics	
Male sex	397 (51.4)
Age at baseline (mo)	22.5 ± 7.1
Age of child at time of assessment (y)	7.83 ± 0.65
Follow-up period (y)	5.95 ± 0.24
HAZ score at baseline	−1.79 ± 1.1
HAZ score at follow-up	−1.02 ± 0.98
Stimulation and learning opportunities	
Child attends school	759 (98.2)
No. of hours/day child plays with other children	1 (1-2)
Child reads story books	153 (19.8)
Child pursues his/her hobby	13 (1.7)
Parents read story books to the child	235 (30.4)
Parents tell stories to the child	344 (44.5)
Parents regularly assist and follow-up with child's studies	673 (87.1)
Family has a fairly regular and predictable schedule for child	339 (43.9)

Data are presented as number (%), mean ± SD or median (IQR).
*General-groups that do not qualify for any of the positive discrimination schemes by Government of India. OBC is a term used by the Government of India to classify castes that are socially and educationally disadvantaged. SC/ST are official designations given to groups of historically disadvantaged indigenous people in India.
†Data not available for 13 mothers.
‡Data not available for 5 fathers.

Baseline HAZ and Cognitive Outcomes

Table II shows the association between baseline HAZ and cognitive outcomes. For the overall sample of children, baseline HAZ was significantly associated with the WISC-CVS z-score (β coefficient [β] 0.08; 95% CI, 0.02-0.14; n = 742), but not the NEPSY-II z-score (β, 0.04; 95% CI, −0.02 to 0.11; n = 741) in the adjusted model. In the subgroup analyses, baseline HAZ was significantly associated with both the WISC-CVS z-score (β, 0.15; 95% CI, 0.08-0.23; n = 447) and the NEPSY-II z-score (β, 0.09; 95% CI, 0.03-0.18; n = 441) among children whose HAZ was measured within 24 months of age. However, this association was not significant among children with baseline HAZ measured after 24 months of age. The interaction between baseline HAZ and age at baseline categories (ie, ≤24 months and >24 months of age) did not reach statistical significance for either the WISC-CVS (P = .36) or the NEPSY-II z scores (P = .77).

Table II. Linear regression models for cognitive scores and baseline HAZ score

Models	WISC-CVS z-score β coefficient (95% CI)	NEPSY z-score β coefficient (95% CI)
Model 1 (unadjusted model)		
Baseline HAZ score	0.27 (0.21 to 0.34); $P < .001$	0.19 (0.13 to 0.26); $P < .001$
Observations	751	750
Model 2 (multivariable model adjusted for covariates)*		
Baseline HAZ score	0.08 (0.02 to 0.14); $P = .006$	0.04 (−0.02 to 0.11)
Observations	742	741
Model 3 (multivariable model adjusted for covariates in subgroup of children with age at baseline ≤24 mo)		
Baseline HAZ score	0.15 (0.08 to 0.23); $P < .001$	0.09 (0.03 to 0.18) ; $P = .039$
Observations	447	441
Model 4 (multivariable model adjusted for covariates in subgroup of children with age at baseline >24 mo)		
Baseline HAZ score	−0.01 (−0.09 to 0.08)	−0.002 (−0.10 to 0.09)
Observations	295	300

Baseline HAZ denotes measurements at the end of the primary trial (ie, at child ages 12-36 months).
*Adjusted for wealth quintile, number of living children in the family, mother's years of schooling, father's years of schooling, father's occupation, and intervention groups in the primary trial. The interaction between baseline HAZ and age at baseline categories (ie, ≤24 months and >24 months of age) was statistically nonsignificant for both WISC-CVS z scores ($P = .36$) and NEPSY z scores ($P = .77$). P values are provided against statistically significant effect sizes.

Change in HAZ between Baseline and Follow-up and Cognitive Outcomes

The HAZ scores at baseline and at the follow-up assessment were strongly correlated (r = 0.74) (**Figure 1**; available at www.jpeds.com). There was also a moderate correlation between change in HAZ and baseline HAZ (r = −0.51) (**Figure 1**). There was no interaction between change in HAZ and baseline HAZ/baseline stunting status for all the cognitive outcomes. Multivariable linear regression models did not show a significant association between change in HAZ scores and the WISC-CVS (β, −0.03; 95% CI, −0.11 to 0.04) or the NEPSY-II z-scores (β, −0.04; 95% CI, −0.12 to 0.06; **Table III**). Similar findings were observed in the subgroup analyses based on baseline stunting status. The perspective plot depicting the relation between baseline HAZ, change in HAZ and WISC-CVS z-score showed that WISC-CVS z-score increases with an increase in baseline HAZ whereas the change in HAZ did not affect the score (**Figure 2**). A similar observation was noted with the NEPSY-II z-score (**Figure 2**).

Change in Stunting Categories and Cognitive Outcomes

Of the total 773 children included in the analysis, 13.1% were in the persistently stunted (n = 101) category, 56.0% were in never stunted (n = 433) category, 30.0% were in the recovered (n = 224) category, and the remaining around 2% were in the faltered (n = 15) category (**Table IV**; available at www.jpeds.com). In the univariate linear regression, compared with children who were persistently stunted, those who recovered from stunting showed significantly higher WISC-CVS and NEPSY-II z-scores (**Table III**). However, in the model with adjustment for covariates, recovery from stunting was not associated with higher WISC-CVS z-score (β, 0.15; 95% CI, −0.05 to 0.34) and NEPSY-II z-score (β, 0.17; 95% CI, −0.05 to 0.39) when compared with children who were persistently stunted. The interaction between change in stunting categories and baseline HAZ was not significant. Additional adjustment for baseline HAZ in the model yielded similar results ie, recovery from stunting was not associated with higher cognitive scores (**Table III**).

Discussion

The current analysis was undertaken to elucidate whether improvement in linear growth beyond the initial 2-3 years of age is associated with higher cognitive outcomes in middle childhood in a follow-up study in North Indian children. We found that approximately two-thirds of the children stunted in early life (68.9%) recovered by late childhood, and linear growth in the first 2 years was associated with cognitive outcomes at 6-9 years of age, even after adjusting for potential confounders. We also observed that increments in HAZ score from early childhood to the late childhood were not associated with higher cognitive scores, thereby suggesting that improvements in linear growth beyond early childhood has limited effects for the cognitive performance in later childhood.

Our findings are in concordance with the recent meta-analysis that documented a positive association between linear growth in the first 2 years of life and cognitive development among children in low- and middle-income countries.[4] However, our findings contrast with studies that recovery from early stunting is associated with improved cognitive outcomes.[10,13,30] Similar to our analyses, these studies adjusted for socioeconomic indicators. However, unlike our analyses, they did not adjust for baseline HAZ, which might confound the observed effect of growth on cognitive development in late childhood. We have shown in our analyses that there is a moderate correlation between baseline HAZ and change in HAZ between early and later childhood. Therefore, baseline HAZ may be adjusted for in these models. In contrast, there is available literature suggesting the potential of bias when adjusting for baseline in analysis of change and further indicating that baseline adjustment substantially

Table III. Linear regression models for cognitive scores with exposures as change in height for age z scores and change in stunting status between baseline (age 12-36 months) and follow-up (age 6-9 years)

Models	WISC-CVS z-score β coefficient (95% CI)	NEPSY z-score β coefficient (95% CI)
Change in height for age z scores between baseline and follow-up		
Model 1 (Unadjusted model)		
Change in HAZ scores	−0.09 (−0.18 to 0.003)	−0.07 (−0.16 to 0.03)
Observations	751	750
Model 2 (multivariable model adjusted for covariates)*		
Change in HAZ scores	−0.03 (−0.11 to 0.04)	−0.04 (−0.12 to 0.06)
Observations	742	741
Model 3 (multivariable model adjusted for covariates and additionally for baseline HAZ)		
Change in HAZ scores	0.03 (−0.06 to 0.12)	0.002 (−0.09 to 0.10)
Observations	742	741
Model 4 (multivariable model adjusted for covariates; stratified by baseline stunting status)		
Nonstunted at baseline		
Change in HAZ scores	0.02 (−0.07 to 0.12)	0.07 (−0.04 to 0.18)
Observations	428	432
Stunted at baseline		
Change in HAZ scores	−0.07 (−0.23 to 0.09)	−0.15 (−0.32 to 0.02)
Observations	314	309
Change in stunting status on cognitive scores		
Model 1 (unadjusted model)		
Persistently stunted	Ref	Ref
Never stunted	0.65 (0.44 to 0.87); $P < .001$	0.55 (0.33 to 0.77); $P < .001$
Recovered	0.33 (0.09 to 0.56); $P = .004$	0.31 (0.07 to 0.55); $P = .004$
Faltered	−0.08 (−0.64 to 0.48)	−0.09 (−0.64 to 0.46)
Observations	751	750
Model 2 (multivariable model adjusted for covariates)*		
Persistently stunted	Ref	Ref
Never stunted	0.21 (0.02 to 0.40); $P = .020$	0.22 (0.01 to 0.43); $P = .031$
Recovered	0.15 (−0.05 to 0.34)	0.17 (−0.05 to 0.39)
Faltered	0.08 (−0.39 to 0.56)	0.11 (−0.40 to 0.62)
Observations	742	741
Model 3 (multivariable model adjusted for covariates and additionally for baseline HAZ)		
Persistently stunted	Ref	Ref
Never stunted	0.05 (−0.21 to 0.31)	0.21 (−0.08 to 0.51)
Recovered	0.09 (−0.11 to 0.30)	0.17 (−0.06 to 0.40)
Faltered	−0.08 (−0.58 to 0.43)	0.11 (−0.44 to 0.66)
Observations	742	741

Baseline denotes child age 12-36 months and follow-up denotes child age 6-9 years.
*Adjusted for wealth quintile, number of living children in the family, mother's years of schooling, father's years of schooling, father's occupation, child schooling, and intervention groups in the primary trial; *P* value for interaction between change in HAZ (between baseline and follow-up) and baseline HAZ as well as baseline stunting status for WISC-CVS and NEPSY z-score not significant; Mean (SE) WISC-CVS z-scores were 0.20 (0.04), −0.55 (0.11), −0.13 (0.07), and −0.54 (0.18) for children belonging to the never stunted, persistently stunted, recovered from stunting, and faltered growth groups, respectively. The mean (SE) NEPSY-II z-scores were 0.16 (0.05), −0.46 (0.10), −0.09 (0.06), and −0.48 (0.17) for the 4 groups, respectively; the *P* value for interaction between change in stunting categories and baseline HAZ for WISC-CVS and NEPSY z scores not significant. *P* values are provided against statistically significant effect sizes.

alters the effect size.[31] Even in studies in which the baseline variable is measured before exposure and could be an important confounder (as in our study), adjustment for this baseline variable may introduce regression-to-the-mean bias.[31] We, therefore, chose to present the analyses with and without adjustment for baseline HAZ scores. In the regression models where we have adjusted for baseline HAZ, the possibility of a biased effect size cannot be ruled out. However, we noted similar findings that increments in HAZ scores from baseline till follow-up as well as recovery from stunting, regardless of whether we adjusted for baseline HAZ or not, were not associated with higher cognitive scores. This finding is visualized in the generalized additive model plots that indicate baseline HAZ, and not the change in HAZ scores, to be related to the outcome scores. Another reason for differences in findings, compared with previous studies, could be that our study measured outcomes related to neuropsychological and general abilities, whereas in other studies measures of school performance (mathematical ability, reading ability and language) were the main outcomes.

Existing evidence supports that linear growth in the first 2 years of life is associated with concurrent and later childhood cognition.[4,7,32-34] The probable explanation could be that the etiology of poor growth and suboptimal neurodevelopment, such as insufficient nutrition; repeated infections and suboptimal care are similar during this period.[35] Although the literature on the associations between early linear growth and cognition is widespread, the literature on the association between catch-up growth after the first 2-3 years and subsequent cognitive development is scarce and conflicting. It is considered that the likelihood of catch-up growth, after the first 2-3 years of life is limited because children remain in environments that contribute to growth restriction.[35] We have shown through our analyses, however, that catch-up growth or recovery from stunting is possible and that 30% of the children in our study sample

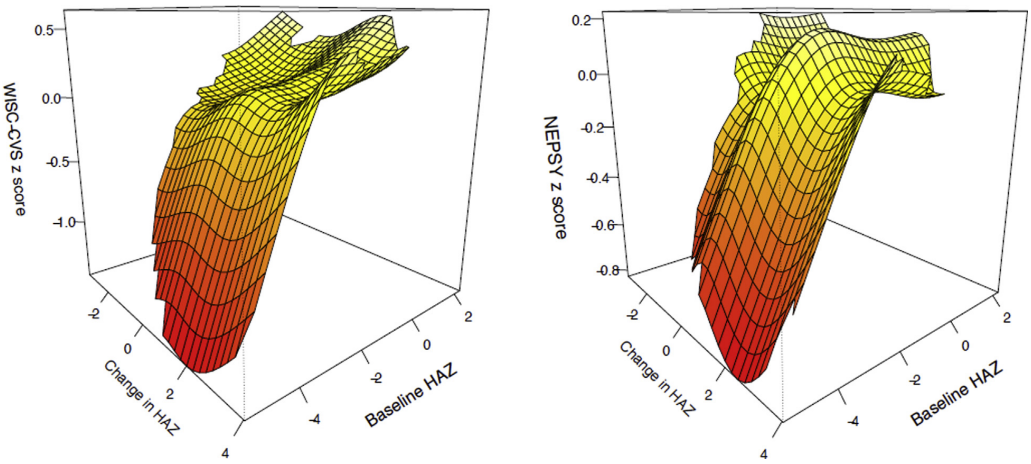

Figure 2. Perspective plot showing the relation between baseline HAZ score, change in HAZ score from early to late childhood and WISC-CVS and NEPSY z-scores.

had recovered from stunting after approximately 6 years. This recovery in stunting status, however, did not lead to higher cognitive abilities of the children when they were in early school age.

Based on a published meta-analysis, we argue the possibility that the factors that affect linear growth and/or cognition in later childhood may either not be similar or they exert a differential effect on these 2 distinct yet related outcomes.[36] The meta-analysis showed that, in nutritional supplementation interventions, improvements in linear growth were associated with small improvements in child development, whereas nurturing and stimulation interventions had significant effects on child development but no effects on linear growth.[36] The review concluded that the determinants of linear growth and neurodevelopment are only partly shared and indicates that improved linear growth may not necessarily be associated with improved cognition. We found substantial attenuation in the association between change in stunting status and cognitive outcomes after adjustment for socioeconomic status, particularly the wealth index created through a principal component analysis.[37] However, we did not find any attenuation after adjustment for the child stimulation variables. Previous studies from India and Vietnam found that stimulation and nurturing environment at home attenuated the association between stunting and cognitive outcomes in children aged ≤24 months, but this effect was not observed in older preschool aged children.[17,18] The children in the current study were older (6-9 years of age), and our result suggest that they had limited sources of stimulation. Owing to limitations of the tool used, we were unable to assess the intensity of the stimulation. These factors might provide some explanation for the observed lack of attenuation effect of stimulation.

The quality of data collected was excellent with closely supervised collection of data on exposures and outcomes by trained and standardized study team members. To depict any nonlinear relationship between change in HAZ, baseline HAZ, and cognitive outcomes, we used a generalized additive model, which adds support to the findings of the study. Despite a long follow-up period (>5 years), we were able to contact and assess approximately 80% of the children enrolled in early childhood. There was approximately a 20% attrition rate. The published article by our group from this follow-up study documented no differences in characteristics between the children who were included in the follow-up and who were not.[22] Therefore, the risk of bias owing to differential loss to follow-up is likely low in our current analysis.

There were some limitations of our analyses. First, growth measurements were available only at few time points, which limited our ability to determine the precise timing of growth improvements beyond the first 2-3 years of age. Second, we used a composite NEPSY-II score rather than scores from the different domains. NEPSY-II is a clinical tool to describe the function of individual domains and is not meant to be a description of global cognitive functioning.[25] As an a priori decision, we used a combined WISC-IV^{INDIA} and CVS z-score based on converted z-scores for the 3 index scores in the WISC-IV^{INDIA} and the total CVS score. This was done because the WISC-IV^{INDIA} verbal comprehension tests required English language skills and CVS was available in Hindi with Indian norms. The ideal scenario would have been to use the WISC-IV^{INDIA} without any changes; however, given the limitations, we believe the adopted methodology provided us with a measure closely reflecting the general ability index (ie, IQ). Third, we did not have reliable data on gestational age; therefore, we could not look at the

differential effect of catch-up growth on cognitive outcomes based on premature, small for gestational age, and term-appropriate for gestation age children. Fourth, we had a very small proportion of children in the faltered category (n = 15 [1.9%]) and, accordingly, reliable insights could not be obtained for this subset of children.

Our findings support the current practice of investing public health efforts to accelerate linear growth in the first 2-3 years of life. Additionally, the findings seem to indicate that much of the effects of catch-up growth on cognitive outcomes are possibly through improvements in socioeconomic status, and considerations of a direct linkage of improved growth with cognitive outcomes should be made with caution. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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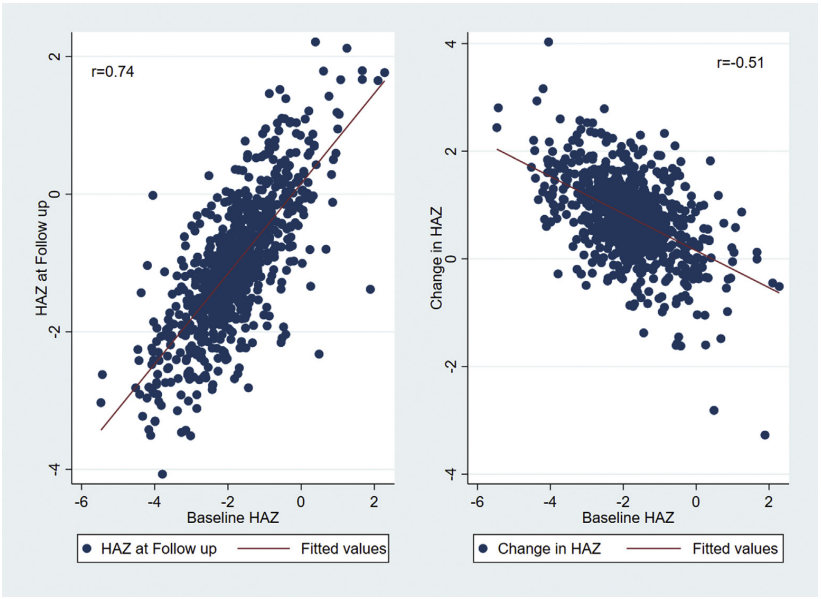

Figure 1. Scatter plot showing the correlation between baseline HAZ and HAZ at follow-up and change in HAZ between early and middle childhood.

Table IV. Baseline characteristics of the study children by stunting categories (n = 773)

Variables	Change in stunting status			
	Never stunted (n = 433)	Persistently stunted (n = 101)	Recovered (n = 224)	Faltered (n = 15)
Sociodemographic characteristics				
Wealth quintile*				
Poorest	56 (12.9)	35 (34.6)	52 (23.2)	5 (33.3)
Very poor	81 (18.7)	25 (24.8)	46 (20.5)	6 (40.0)
Poor	73 (16.9)	24 (23.8)	57 (25.5)	3 (20.0)
Less poor	99 (22.9)	13 (12.9)	45 (20.1)	0 (0.0)
Least poor	124 (28.6)	4 (3.9)	24 (10.7)	1 (6.7)
Religion				
Hindu	362 (83.6)	85 (84.2)	182 (81.3)	14 (93.3)
Muslim	58 (13.4)	15 (14.9)	37 (16.5)	1 (6.7)
Others (Jain/Sikh/Christian)	13 (3.0)	1 (0.9)	5 (2.2)	0 (0.0)
Social class*,†				
Scheduled caste/scheduled tribe	187 (43.2)	63 (62.4)	129 (57.6)	12 (80.0)
Other backward class	86 (19.9)	17 (16.8)	43 (19.2)	2 (13.3)
General class	160 (36.9)	21 (20.8)	52 (23.2)	1 (6.7)
Mother's age in completed years	31.7 ± 4.7	31.2 ± 4.9	31.4 ± 5.1	30.7 ± 6.0
Mother's years of schooling*				
Median (IQR)	8 (3-12)	5 (0-8)	6 (0-9)	0 (0-5)
Mean ± SD	7.7 ± 5.3	4.7 ± 4.4	5.9 ± 4.4	1.8 ± 3.2
Mother's working status*,‡				
Works outside home	74 (17.4)	26 (26.3)	31 (14.1)	5 (33.3)
Does not work outside home	352 (82.6)	73 (73.7)	189 (85.9)	10 (66.7)
Father's years of schooling*				
Median (IQR)	10 (8-12)	8 (5-10)	8 (5.5-10)	8 (5-9)
Mean ± SD	9.7 ± 4.1	7.1 ± 3.8	7.8 ± 4.2	6.9 ± 3.6
Father's occupation*,§				
Government or private job	239 (55.6)	51 (51.0)	125 (55.8)	6 (42.9)
Daily wage earner	42 (9.8)	25 (25.0)	44 (19.6)	6 (42.9)
Self-employed	133 (30.9)	18 (18.0)	47 (21.0)	2 (14.2)
Unemployed	16 (3.7)	6 (6.0)	8 (3.6)	0 (0.0)
Type of family				
Nuclear	252 (58.2)	60 (59.4)	127 (56.7)	9 (60.0)
Joint	181 (41.8)	41 (40.6)	97 (43.3)	6 (40.0)
No. of living children in the family*				
1	34 (7.9)	5 (4.9)	6 (2.7)	1 (6.7)
2-3	321 (74.1)	59 (58.4)	159 (71.0)	10 (66.7)
≥4	78 (18.0)	37 (36.7)	59 (26.3)	4 (26.6)
Family has television at home	424 (97.9)	96 (95.1)	221 (98.7)	14 (93.3)
Family buys newspaper*	84 (19.4)	7 (6.9)	21 (9.4)	1 (6.7)
Child characteristics				
Sex				
Male	213 (49.2)	54 (53.5)	122 (54.5)	8 (53.3)
Female	220 (50.8)	47 (46.5)	102 (45.5)	7 (46.7)
Age at baseline (mo)*	22.4 ± 7.2	23.6 ± 6.9	22.7 ± 6.9	18.2 ± 6.2
Age of child at time of follow-up assessment (mo)*	94.0 ± 8.1	94.9 ± 7.6	93.9 ± 7.2	88.3 ± 6.6
Months of follow-up	71.6 ± 2.9	71.4 ± 3.3	71.3 ± 2.5	70.1 ± 2.3
HAZ score at baseline*	−1.06 ± 0.77	−3.25 ± 0.74	−2.57 ± 0.46	−1.28 ± 0.70
HAZ score at follow-up*	−0.46 ± 0.76	−2.56 ± 0.43	−1.31 ± 0.45	−2.29 ± 0.25
Stimulation and learning opportunities				
Child attends school*				
Yes and at a private school	285 (65.8)	44 (43.6)	129 (57.6)	5 (33.3)
Yes and at a government school	142 (32.8)	52 (51.5)	93 (41.5)	9 (60.0)
Does not attend school	6 (1.4)	5 (4.9)	2 (0.9)	1 (6.7)
No. of hours/day child plays with other children*				
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	2 (1-2)
Mean ± SD	1.28 ± 0.8	1.26 ± 0.8	1.34 ± 0.8	2.01 ± 1.7
Child reads story books	90 (20.8)	18 (18.0)	42 (18.8)	3 (20.0)
Child pursues his/her hobby	8 (1.9)	3 (2.9)	2 (0.9)	0 (0.0)
Parents read story books to the child*				
Yes (daily or on alternate days)	83 (19.2)	7 (7.0)	39 (17.4)	1 (6.7)
Yes (weekly or monthly)	66 (15.2)	10 (10.0)	27 (12.1)	2 (13.3)
Do not read story books	284 (65.6)	83 (83.0)	158 (70.5)	12 (80.0)
Parents tell stories to the child				
Yes (daily or on alternate days)	106 (24.5)	15 (14.8)	50 (22.3)	4 (26.7)

(*continued*)

Table IV. Continued

Variables	Change in stunting status			
	Never stunted (n = 433)	Persistently stunted (n = 101)	Recovered (n = 224)	Faltered (n = 15)
Yes (weekly or monthly)	102 (23.6)	24 (23.8)	41 (18.3)	2 (13.3)
Do not tell stories	225 (51.9)	62 (61.4)	133 (59.4)	9 (60.0)
Parents regularly assist and follow-up with child's studies*				
Yes (daily or on alternate days)	373 (86.1)	73 (73.0)	180 (80.4)	11 (78.6)
Yes (weekly or monthly)	17 (3.9)	8 (8.0)	11 (4.9)	0 (0.0)
Do not assist	43 (10.0)	19 (19.0)	33 (14.7)	3 (21.4)
Family has a fairly regular and predictable schedule for child*	202 (46.7)	41 (40.6)	94 (42.0)	2 (13.3)

Data are presented as number (%), mean ± SD or median (IQR).
*Difference in proportions/mean between the groups is statistically significant (ie, $P < .05$).
†General is the group that does not qualify for any of the positive discrimination schemes by Government of India. OBC is a term used by the Government of India to classify castes that are socially and educationally disadvantaged. SC/ST are official designations given to groups of historically disadvantaged indigenous people in India.
‡Data are not available for 13 mothers.
§Data are not available for 5 fathers.

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RESEARCH

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Early child stimulation, linear growth and neurodevelopment in low birth weight infants

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Abstract

Background: Children with low birth weight (LBW) are at risk of linear growth faltering and developmental deficits. Evidence suggests that early child stimulation and care reflected as responsive caregiving and opportunities for learning can promote development. The current analysis aimed to measure the extent to which linear growth and early child stimulation modify each other's association with neurodevelopmental outcomes among LBW infants.

Methods: This is a secondary data analyses from a randomized controlled trial on the effect of community-initiated kangaroo mother care in LBW infants on their neurodevelopment at 12 months of corrected age. Bayley Scales of Infant and Toddler Development was used to assess cognitive, motor and language scores. Stimulation at home was assessed by the Pediatric Review of Children's Environmental Support and Stimulation (PROCESS) tool. PROCESS scores were categorized into three groups: < Mean-1SD (*low stimulation)*; Mean ± 1 SD (*moderate stimulation)* and > mean + 1SD (*high stimulation)*.

Results: A total of 516 infants were available for neurodevelopment assessments. Interactions were observed between length for age z-score (LAZ) and PROCESS score categories. In the low stimulation group, the adjusted regression coefficients for the association between LAZ and cognitive, motor and language scores were substantially higher than in the moderate and high stimulation group. Stimulation was positively associated with neurodevelopmental outcomes in both stunted and non-stunted infants; however, the association was twice as strong in stunted than in non-stunted.

Conclusion: Moderate to high quality stimulation may alleviate the risk of sub-optimal development in LBW infants with linear growth deficits.

Clinical trial registration: The primary trial whose data are analysed is registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02631343).

Keywords: Linear growth, Child stimulation, Neurodevelopment, Low birth weight, Infancy

What is already known on this topic?

- Linear growth and quality of stimulation and nurturance are independently known to influence neurodevelopment, especially in children born with low birth weight (LBW).

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- The extent to which growth and stimulation influence each other's association with cognitive, motor and language scores is unknown.

What this study adds?

- High quality stimulation and nurturance could protect LBW infants with growth deficits from poor development scores.
- Association of stimulation with neurodevelopmental outcomes was twice as strong in stunted than in non-stunted infants.

Introduction

The first 1000 days i.e., from conception through age 24 months, are foundational for brain development [1]. Both adverse and positive experiences during this period may critically shape children's developmental trajectories [2, 3]. Children born with low birth weight (LBW) are at risk of linear growth faltering, cognitive and motor deficits as well as lower academic performance and behavioural problems compared to their normal birth weight counterparts [4–7]. Linear growth faltering in the first 2 years of life has been shown to be negatively associated with cognitive performance in childhood [8, 9]. There is also strong evidence that a child's positive home environment reflected as responsive caregiving and opportunities for early learning, can promote development [10–12].

Less is known on whether linear growth and quality of stimulation/responsive caregiving at home influence each other's association with cognitive, motor and language scores. Using a sample of 513 infants from rural India, Black et al. showed that a nurturant home environment attenuated associations between linear growth and fine motor and receptive language development [13]. Similarly, another multicentre study from Burkina Faso, Ghana and Malawi did not detect significant association between linear growth faltering and child development in the context of a high-quality developmental stimulation [14]. A study from rural Vietnam noted a modest beneficial effect of early child development interventions on cognition among children with declining height-for-age Z-scores or those that were stunted [15]. These findings indicate that in the presence of an environment characterized by nurturance and learning opportunities, children with low length-for- age z score (LAZ) can acquire developmental skills at the same level as their peers. Contrasting these findings, recent studies from Malaysian and Jamaican infants found no significant influence of home environment quality on the association between LAZ status and cognitive outcomes [16, 17]. More evidence is required on the interactive effects of linear growth and home environment in relation to developmental outcomes, particularly for the vulnerable subset of LBW infants. Further, evidence is required on whether in a setting with socio-economic constraints, a moderate to high-quality home environment can protect LBW infants with growth deficits from poor development scores and whether there is a differential effect of stimulation on developmental outcomes based on whether the LBW infant is stunted or not. The present analysis was aimed at providing insights on these pertinent issues of global importance.

Methods

Study design and participants

This secondary data analysis was conducted using data from an individually randomized controlled trial (RCT) aimed to evaluate the effect of community-initiated Kangaroo Mother Care (ciKMC) on neurodevelopmental outcomes of infants born low birth weight at 12 months of corrected age (ClinicalTrials.gov identifier NCT02631343) [18]. The study was conducted in resource constrained settings of rural and semi-urban Haryana, North India. In this study population, ciKMC was not associated with the neurodevelopment measures at 12 months [18]. A total of 552 stable preterm or small for gestational age term infants identified within 72 hours of birth and weighing between 1500 and 2250 g were included in the trial and followed up till 12 months of age. In the primary trial, infants weighing between 1500 and 1800 g, as per the government recommendations, were initially referred to a health facility for evaluation. These infants were considered for inclusion only if the families refused to take the baby to the health facility, or if the baby was taken but the medical doctor/paediatrician did not recommend admission or if admission was done, it was for less than 72 hours [18]. The primary trial excluded infants who were unable to feed, had difficulty in breathing, had less than normal movements and those with gross congenital malformations. As this was a trial assessing the efficacy of Kangaroo Mother Care (KMC) initiated at home/community, those infants who had KMC initiated at the health facility were excluded [18].

Details of the trial have been published elsewhere [18, 19]. Ethical clearances for the primary trial were obtained from the Institutional Ethics Review Committee of Society for Applied Studies, New Delhi (SAS/ERC/KMC-GCC/2015), the World Health Organization (WHO) Ethics Review Committee, Geneva (ERC0002629) and the Regional Committee for Medical and Health Research Ethics in Norway. In the primary trial, written informed consent was obtained from all subjects and/or their legal guardian(s).

Exposure and outcomes

Baseline information was collected on maternal and paternal age and education, birth order, parity and sex of the infant. Gestational age was documented from an ultrasound report, hospital records or maternal recall, whichever was available, in the given order of preference. The wealth of the family was determined by an index created through a principal component analysis based on household assets [20]. Information on vital status, illnesses (including any hospitalization) along with anthropometric measurements (weight and length) were captured by an independent trained team during their home visits at infant age 1, 3, 6 and 12 months. Caregivers were asked about illness (es) and hospitalization(s) in the 2 weeks preceding the visit. Length was measured using infantometers reading to the nearest 0.1 cm. Exclusivity of breastfeeding was assessed at 1, 3 and 6 months of infant age through a structured questionnaire.

Developmental outcomes were ascertained in the study clinic by trained psychologists using the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) at 12 months of corrected age [21]. The BSID-III was adapted for use in the study setting. Details of the adaptation have been provided elsewhere [18]. Child stimulation at home was assessed at 12 months of age by trained psychologists using "Pediatric Review of Children's Environmental Support and Stimulation (PROCESS)" questionnaire [22–24]. PROCESS was created for use with parents of children 2–18 months of age and can be administered in a clinic or in a home setting [22]. It consists of three components: a parent questionnaire, clinical observation, and a toy checklist. The parent questionnaire includes 24 items about the physical environment, household organization, and stimulation practices for development. The 20 observational items focus primarily on the emotional quality of parent-child interactions and the toy checklist consists of 40 items. Total scores are summed across the three sections [22]. Higher scores reflect better stimulation and support to infants. PROCESS scores have been shown to have a good correlation ($r = 0.84$) with the most widely used measure of the household environment i.e., Home Observation for Measurement of the Environment (HOME) scores [23, 24].

Plan of analyses

All analyses were done using STATA version 16.0 and R version 3.3.3 (2017-03-06). Baseline characteristics were summarized as mean (SD) or proportion. Length-for-age z score (LAZ) was calculated based on the WHO Child Growth Standards, using the zanthro package in STATA [25]. Stunting was defined as LAZ < -2, based on the standard WHO definition [25]. Length measurements were done at 1, 3 and 6 and 12 months of infant age. For this analysis, we preferred to use the length measurements at 6 months instead of 12 months as we wanted to look at the interactions in a cohort approach rather than cross sectionally. Another related premise for adopting such an approach in mid-infancy was that if we could show that linear growth and stimulation at home interacted with each other and influenced each other's association with neurodevelopment outcomes at 12 months of age, this would provide a reasonable time frame for the caregivers with infants having growth failure to invest in stimulation at home for improving their child's neurodevelopment. PROCESS scores, reflecting stimulation environment at home, were categorized into three groups: *Low stimulation group* (< Mean-1SD); *moderate stimulation group* (Mean ± 1 SD) and *high stimulation group* (> Mean + 1SD). The mean (SD) PROCESS score was 124 (18).

Neurodevelopmental outcomes consisted of cognitive, motor and language composite scores assessed by BSID-III at 12 months of corrected age. We first measured the association of LAZ at 6 months and PROCESS scores with scores obtained on BSID-III. We selected covariates for adjustment in the model based on their biological plausibility to influence the exposure and the outcomes and purposive selection principle i.e., covariates that brought at least 15% change in the univariate beta-coefficient were included in the multivariable model [26, 27].

We assessed the interaction between LAZ scores at 6 months of age and the PROCESS scores using likelihood ratio test comparing models with and without interaction terms. Analyses were stratified following the identification of a possible interaction. We initially did a screening where a *P*-value for interaction of less than 0.20 was investigated further [28]. The investigation was focussed on examining whether the magnitude of association between LAZ and outcome(s) of interest differed between the subgroups based on PROCESS score categories. Stratified results were presented at differing levels of PROCESS scores (low, moderate and high stimulation). For each of the categories of PROCESS score, we used linear regression with the composite scores for cognition, motor or language as an outcome and LAZ score as the exposure variable. Selection of variables for adjustment in the models was based on biological plausibility and purposive selection principle [26, 27].

Similarly, to assess whether the association between PROCESS scores and neurodevelopmental outcomes was modified by whether the babies were stunted or not, the interaction between the PROCESS score categories and stunting status was assessed using likelihood ratio test comparing models with and without interaction terms.

In instances where the *P*-value of interaction was less than 0.20, the analyses were stratified and the effect sizes for the association between PROCESS categories and outcome(s) of interest were presented by the stunting categories. We used generalized additive models (GAM) in the *mgcv package* in R statistical package to depict non-linear associations between PROCESS score, LAZ and outcome scores (composite cognitive, motor and language scores) [29].

Ethics approval

No ethical approval was required for this secondary data analysis. However, the authors obtained written permission from the principal investigator of the primary trial to use the data for this secondary analysis.

Results

Characteristics of the sample

The primary trial enrolled 552 infants of which 516 infants had their neurodevelopment assessment at 12 months of age. The remaining 36 infants either died ($n=29$) or the families had moved out of the study area ($n=7$). Baseline characteristics of the 516 infants that were included in this analysis have been presented in Table 1. Supplementary Table 1 presents the comparison of baseline variables between infants with neurodevelopment assessment at 12 months of age and those that did not have the assessment and indicates no statistically significant differences. The infants studied belonged to economically constrained settings as reflected by some of the indicators such as proportion below poverty line (around 23%; national figure of around 15%) and median yearly family income (1316 USD; for some of the developed countries like United States, of around 67,000 USD) [30, 31].

The mean (SD) composite cognitive, motor and language scores of the sample were 102.1 (11.8), 90.2 (10.4) and 84.9 (9.1) respectively. A total of 52.5% (271/516) of the infants were stunted at 6 months of age. As the exposures of interest i.e., linear growth at 6 months of age and PROCESS scores at 12 months of age were measured after the original intervention (ciKMC) was delivered, we attempted to understand whether ciKMC influenced these exposures. The mean (SD) PROCESS score at 12 months of age was statistically similar in the intervention [123.0 (16.6)] and control [125.0 (16.5)] groups ($P=0.16$). Further, the mean (SD) LAZ at 6 months of age was also statistically similar in the intervention [−2.12 (1.04)] and control [−2.09 (1.06)] groups ($P=0.72$). The ciKMC intervention did not have any significant association with the cognitive, language and motor outcomes at 12 months of adjusted age [18].

Table 1 Baseline characteristics of the infants included in this secondary data analysis ($N=516$)

Variables	Number (%)
Household characteristics	
Yearly family income (in USD); Median (IQR)	1316 (948–2368)
Proportion of families below poverty line	122 (23.7)
Religion	
Hindu	423 (81.9)
Muslim	89 (17.3)
Others [a]	4 (0.8)
Social class [b]	
General	133 (25.8)
Other Backward Class (OBC)	167 (32.4)
Scheduled Caste/Tribe (SC/ST)	216 (41.8)
Type of family	
Nuclear	135 (26.2)
Joint	381 (73.8)
Maternal and paternal characteristics	
Mean maternal age (years; SD)	23.1 (3.8)
Median years of education of mother (IQR)	5 (0–9)
Mother's occupation	
Home maker	507 (98.3)
Mean father's age (years; SD)	26.4 (4.7)
Median years of education of father (IQR)	8 (5–12)
Birth related characteristics	
Place of delivery	
Home	148 (28.7)
Government facility	266 (51.5)
Private facility	102 (19.8)
Type of delivery	
Normal vaginal [c]	511 (99.0)
Birth order	
1	191 (37.0)
2–3	232 (45.0)
≥4	93 (18.0)
Parity	
Primiparous	191 (37.0)
Infant characteristics	
Sex of the baby	
Male	208 (40.3)
Mean birth weight (grams, SD)	2058.7 (165.3)
Birth weight (range; in grams)	1550–2250
Mean gestational age (weeks, SD)	35.7 (1.9)
Gestational age (range; in weeks)	24–40
Early initiation of breastfeeding (within an hour of birth) present	323 (62.6)
Exclusive breastfeeding at 3 months	250 (48.4)

[a] Others: Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist

[b] General- group that do not qualify for any of the positive discrimination schemes by Government of India (GOI), OBC- term used by the Government of India to classify castes which are socially and educationally disadvantaged, SC/ST- official designations given to groups of historically disadvantaged indigenous people in India

[c] normal unassisted vaginal delivery; USD- United States Dollar; SD- standard deviation; IQR- Inter-quartile range

LAZ, PROCESS score and cognitive outcome

LAZ and PROCESS scores were associated with cognitive scores (Table 2).

There was an interaction between LAZ and PROCESS score categories for the cognitive composite score ($P=0.08$) (Table 3).

In the low stimulation group, the adjusted regression coefficient ($b=3.63$, 95% CI; 1.22, 6.03) was substantially higher than in the moderate stimulation group ($b=1.41$, 95% CI; 0.25, 2.56) and the high stimulation group ($b=1.69$, 95% CI; −1.15, 4.52) (Table 3). The GAM plot supports the findings obtained in regression models (Fig. 1). The GAM plot shows that at lower PROCESS scores, the cognitive scores tend to decrease with decrease in LAZ scores whereas at higher PROCESS scores, the relation between LAZ and cognitive score has low variability. Further, with an increase in the PROCESS scores, the cognitive scores increased, more so in those with LAZ less than −2 SD. An interaction was observed between stunting and PROCESS score categories (Table 4).

In both stunted and non-stunted infants, PROCESS scores were associated with cognitive scores with a clear dose response relationship (Table 4). The adjusted regression coefficient was comparatively higher in stunted infants.

LAZ, PROCESS score and motor outcome

LAZ and PROCESS scores were associated with motor scores (Table 2). There was an interaction between LAZ and PROCESS score categories for the motor composite score ($P=0.03$) (Table 3). In the low stimulation group, the adjusted regression coefficient ($b=4.08$, 95% CI; 1.69, 6.46) was higher than in the moderate stimulation ($b=1.54$, 95% CI; 0.50, 2.58) and the high stimulation group ($b=1.05$, 95% CI; −1.14, 3.25) (Table 3). The GAM plot confirmed the findings obtained in regression models (Fig. 1). An interaction was observed between stunting and PROCESS score categories (Table 4). In stunted infants, PROCESS scores were associated with motor composite scores with a dose response relationship. In non-stunted infants, the adjusted regression coefficient was comparatively lower and did not reach statistical significance.

LAZ, PROCESS score and language outcome

LAZ and PROCESS scores were associated with language scores (Table 2). A potentially relevant interaction ($P=0.12$) was observed between LAZ and PROCESS score categories (Table 3). In the low stimulation group, the adjusted regression coefficient ($b=2.47$, 95% CI; 0.56, 4.38) was substantially higher than in the moderate stimulation ($b=1.02$, 95% CI; 0.21, 1.86) and high stimulation group ($b=0.40$, 95% CI; −1.78, 2.58) (Table 3). The GAM plot confirmed the findings obtained in regression models (Fig. 1). An interaction was observed between stunting and PROCESS score categories ($P=0.05$) (Table 4). In both stunted and non-stunted infants, PROCESS scores were associated with language scores with a distinct dose response relationship. The adjusted regression coefficient was comparatively higher in stunted infants.

Discussion

The current analyses aimed at providing answers to questions with programmatic implications, specifically whether within a setting with socio-economic constraints, a moderate to high-quality home environment can alleviate the risk of low development scores in LBW infants with linear growth deficits. We observed a weakening of the association between growth deficits and

Table 2 Association of length for age z score (LAZ) and PROCESS score with cognitive, motor and language scores at 12 months of corrected age ($N=516$)

Variables	Cognitive score	Motor score	Language score
	Adjusted mean difference, b (95% CI) [a]; *p* value		
LAZ at 6 months	1.78 (0.74, 2.83); $p=0.001$	2.02 (1.11, 2.94); $p<0.001$	1.15 (0.37, 1.93); $p=0.004$
Stunting status at 6 months			
Non-stunted	Ref	Ref	Ref
Stunted	−2.99 (−5.11, −0.87); $p=0.006$	−3.42 (−5.28, −1.55); $p<0.001$	−2.53 (−4.11, −0.95); $p=0.002$
PROCESS score at 12 months	0.25 (0.18, 0.31); $p<0.001$	0.16 (0.10, 0.22); $p<0.001$	0.22 (0.17, 0.27); $p<0.001$
PROCESS categories			
< Mean-1 SD (Low)	Ref	Ref	Ref
Mean ± 1 SD (Moderate)	9.52 (6.47, 12.56); $p<0.001$	6.60 (3.85, 9.36); $p<0.001$	7.76 (5.53, 9.99); $p<0.001$
> Mean + 1SD (High)	12.94 (8.95, 16.95); $p<0.001$	8.60 (4.98, 12.23); $p<0.001$	11.82 (8.89, 14.76); $p<0.001$

[a] Adjusted for wealth quintile, gestational age, birth weight, mother's education, birth order, exclusive breastfeeding at 3 months, study groups (intervention and control) and hospitalization for severe illness

Table 3 Association between length for age z score and neurodevelopmental outcomes, by PROCESS score categories

Variable	*N* = 516		
	Adjusted regression coefficient (b) [a]	**95% CI**	***P*-value**
Cognitive composite score (*P*-value for interaction between PROCESS score categories and LAZ score = 0.08)			
In low stimulation group (*n* = 72)			
LAZ score	3.63	1.22, 6.03	0.004
In moderate stimulation group (*n* = 367)			
LAZ score	1.41	0.25, 2.56	0.02
In high stimulation group (*n* = 77)			
LAZ score	1.69	−1.15, 4.52	0.24
Motor composite score (*P*-value for interaction between PROCESS score categories and LAZ score = 0.03)			
In low stimulation group (*n* = 72)			
LAZ score	4.08	1.69, 6.46	0.001
In moderate stimulation group (*n* = 367)			
LAZ score	1.54	0.50, 2.58	0.004
In high stimulation group (*n* = 77)			
LAZ score	1.05	−1.14, 3.25	0.34
Language composite score (*P*-value for interaction between PROCESS score categories and LAZ score = 0.12)			
In Low stimulation group (*n* = 72)			
LAZ score	2.47	0.56, 4.38	0.01
In moderate stimulation group (*n* = 367)			
LAZ score	1.02	0.21, 1.86	0.02
In high stimulation group (*n* = 77)			
LAZ score	0.40	−1.78, 2.58	0.72

[a] Adjusted for wealth quintile, maternal age, maternal education, father's age, father's education, parity, birth order, sex of the infant, gestational age, exclusive breastfeeding at 3 months, study groups (intervention and control) and hospitalization for severe illness during infancy; Low stimulation group (PROCESS score; < Mean-1SD); moderate stimulation group (PROCESS score; Mean ± 1 SD) and high stimulation group (PROCESS score; > Mean + 1SD)

LAZ Length for age Z score, *PROCESS* Pediatric Review of Children's Environmental Support and Stimulation, *SD* Standard Deviation

negative neurodevelopment outcome with increase in stimulation and nurturance at home. Additionally, we also observed that while stimulation at home was associated with neurodevelopmental outcomes in both stunted and non-stunted infants, the association was stronger in stunted than non-stunted infants.

Our findings corroborate the studies done in Bangladesh, Vietnam and in African settings (Burkina Faso, Malawi and Ghana) where the authors noted that among non-low birth weight children, a nurturant home environment attenuated the association between linear growth and neurodevelopmental outcomes [13–15]. However, findings contrast with the results of the studies among the Malaysian and Jamaican children where no significant influence of home environment quality on the association between LAZ status and cognitive outcomes was noted. The observed difference might be due to fairly smaller sample sizes in these studies, thereby reducing the power to detect significant interactions [16, 17].

There is lack of consensus with regards to the consideration of *P*-value to indicate presence of an interaction. While some investigators propose to adhere to the conventional *P*-value of < 0.05, others suggest that usually the power to test for interactions is low in many epidemiologic studies and therefore, testing for interaction tests based solely on *P*-value of < 0.05 may be misleading and could probably miss out important effect modifications [28, 32–34]. Based on this consideration, the suggestion is to increase the type 1 error rate to 20% while assessing tests of interaction [28]. Some researchers argue that consideration of a *P*-value for interaction tests is a part of the entire spectrum of information to be utilized in the assessment of effect modification and other components should be considered such as stratum-specific measures and prior biological knowledge [35, 36]. In our study, we considered a *P*-value of less than 0.20 to further investigate for

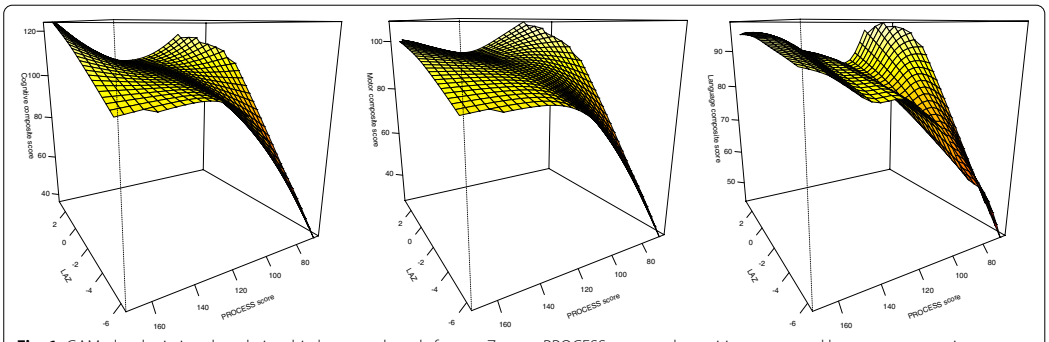

Fig. 1 GAM plot depicting the relationship between length-for-age Z score, PROCESS score and cognitive, motor and language composite score

Table 4 Association between PROCESS score categories and neurodevelopmental outcomes, by stunting status

Variable	*N* = 516		
	Adjusted regression coefficient (b) [a]	95% CI	*P*-value
Cognitive composite score (*P*-value for interaction between PROCESS score categories and stunting categories = 0.17)			
LAZ < -2 (*n* = 271)			
Low stimulation	Ref		
Moderate stimulation	11.09	7.26, 14.92	< 0.001
High stimulation	15.17	9.66, 20.68	< 0.001
LAZ ≥ −2 (*n* = 245)			
Low stimulation	Ref		
Moderate stimulation	6.37	1.77, 10.97	0.007
High stimulation	9.31	3.54, 15.08	0.002
Motor composite score (*P*-value for interaction between PROCESS score categories and stunting categories = 0.12)			
LAZ < -2 (*n* = 271)			
Low stimulation	Ref		
Moderate stimulation	8.19	4.49, 11.88	< 0.001
High stimulation	11.76	6.44, 17.06	< 0.001
LAZ ≥ −2 (*n* = 245)			
Low stimulation	Ref		
Moderate stimulation	3.28	−0.53, 7.09	0.09
High stimulation	4.24	−0.54, 9.03	0.08
Language composite score (*P*-value for interaction between PROCESS score categories and stunting categories = 0.05)			
LAZ < -2 (*n* = 271)			
Low stimulation	Ref		
Moderate stimulation	9.26	6.58, 11.95	< 0.001
High stimulation	14.19	10.32, 18.05	< 0.001
LAZ ≥ −2 (*n* = 245)			
Low stimulation	Ref		
Moderate stimulation	4.29	0.82, 7.75	0.02
High stimulation	7.48	3.13, 11.83	0.001

[a] Adjusted for wealth quintile, maternal age, maternal education, father's age, father's education, parity, birth order, sex of the infant, gestational age, exclusive breastfeeding at 3 months, study groups (intervention and control) and hospitalization for severe illness during infancy; Low stimulation (PROCESS score; < Mean-1SD); moderate stimulation (PROCESS score; Mean ± 1 SD) and high stimulation (PROCESS score; > Mean + 1SD)

LAZ Length for age Z score, *PROCESS* Pediatric Review of Children's Environmental Support and Stimulation, SD Standard Deviation

potential interaction. Subsequently, we placed emphasis on the magnitude of effect size within the subgroups and attempted to make careful interpretations. Our findings were also supported by the GAM plots that depicted non-linear relationships between LAZ, PROCESS score and neurodevelopment outcomes.

There are strengths and limitations of this secondary data analyses. The data utilized is from a robust and well conducted randomized controlled trial with very low attrition. The measurements, including the anthropometry, and outcome data were collected by trained and standardized study team. One of the limitations is that the study lacks reliable data on gestational age. Weight was measured within 72 hours of birth by trained study team and inclusion of infants with weight between 1500 and 2250 g meant that these infants would be either preterm or term small for gestational age. Therefore, the findings could be extended only to a specific population of LBW infants i.e., stable late preterm or term small for gestational age (SGA) infants. There could also be a possibility that in babies with poorer linear growth or smaller attained length at 6 months of age or rather the factors that lead to such growth faltering may lead to poorer home stimulation which is measured 6 months later by PROCESS. Measurement of home stimulation at one time point only i.e., at 12 months is also a limitation. We also acknowledge that this being an observational study, the results may be affected by unmeasured confounding.

Our findings support the promotion of stimulation to LBW infants in order to offset the negative effect of growth faltering on neurodevelopmental outcomes. It is likely that every child will benefit from this strategy and therefore, future studies should test this approach in normal/non-high-risk children as well. Our findings indicate that through focusing only on nutrition for growth, we may miss to capitalize the important developmental effects of early child stimulation and responsive caregiving. The findings call for a comprehensive approach with nutrition and nurturing care at the forefront. This approach underlies the comprehensive framework of Nurturing Care that incorporates health, nutrition, responsive caregiving, opportunities for early learning, and child protection as a way to help children not only survive but also thrive [37].

Conclusion

The findings suggest that a moderate to high-quality stimulation at home may alleviate the risk of poor development scores in LBW infants with linear growth deficits. Early child stimulation may particularly be beneficial for LBW infants with linear growth deficits/stunting. Efforts for improving child development should be comprehensive with promotion of adequate nutrition and optimal nurturing care as integral components.

Abbreviations

LBW: Low birth weight; PROCESS: Pediatric Review of Children's Environmental Support and Stimulation tool; LAZ: Length for age Z score; RCT: Randomized controlled trial; CiKMC: Community initiated Kangaroo Mother Care; HBPNC: Home Based Post Natal Care; BSID-III: Bayley Scales of Infant and Toddler Development, 3rd Edition; HOME: Home Observation for Measurement of the Environment; GAM: Generalized additive models; SGA: Small for gestational age; AGA: Appropriate for gestational age.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-022-03579-6.

Additional file 1: Supplementary Table 1. Comparison of baseline characteristics of the infants with neurodevelopment data at 12 months ($N=516$) and those that did not have ($N=36$).

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None.

Authors' contributions
RPU, ST, TAS and MH were involved in conceptualization, data acquisition, analysis, interpretation of data and drafting of the manuscript. ST, NB and SM were involved in designing and conducting the primary trial. NB and SM also provided administrative and technical support for this secondary data analysis exercise. HS, JM, TD, PK and RB provided critical feedback on the statistical analysis and drafting of the manuscript. All authors critically reviewed the manuscript, provided important intellectual content and approved the final manuscript as submitted. The authors agree to be accountable for all aspects of the work.

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The authors have no financial relationship relevant to this article to disclose RB and TD are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the World Health Organization.

Availability of data and materials
The dataset analysed in the present study is publicly available at: https://figshare.com/s/c932d11ff5101e2268bf.

Declarations

Ethics approval and consent to participate
No ethical approval was required for this secondary data analysis. However, the authors obtained written permission from the principal investigator of the primary trial to use the data for this secondary analysis. Ethical clearances for the primary trial were obtained from the Institutional Ethics Review Committee of Society for Applied Studies, New Delhi, the World Health Organization (WHO) Ethics Review Committee, Geneva and the Regional Committee for Medical and Health Research Ethics in Norway.

Consent for publication
Not applicable.

Competing interests
No competing interest to declare.

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