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Linear growth and child development during early childhood in Bangladesh

By

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Degree to be awarded: MPH

Global Epidemiology

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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology

2019

Abstract

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By Kaustubh Wagh

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Design: Prospective longitudinal cohort study with structured home interviews during pregnancy and 3, 9, 16 and 24 mo after delivery.

Setting: Two rural sub-districts (Karimganj; Katiadi) of Kishoreganj district, Bangladesh.

Subjects: Mother-infant dyads.

Results: We observed decrease in mean length-for-age Z (LAZ) scores from -1.1 at 3 mo to -2.3 at 24 mo. Similar trend was observed in head circumference z-scores (HCZ) although BMI z-scores (BMIZ) remained constant between 3 to 24 mo. For one unit increase in LAZ score at 3 mo, the motor z-score at 9 mo increased by 0.10 (95% CI 0.07, 0.14). Similarly, one unit change in LAZ score at 9 mo and 16 mo was associated with increase in motor z-scores at 16 mo and 24 mo by 0.16 (95% CI 0.12, 0.20) and 0.12 (95% CI 0.08, 0.16) respectively. Additionally, for one unit increase in LAZ score at 9 and 16 mo, the cognitive z-score at 16 and 24 mo was increased by 0.12 (95% CI 0.08, 0.16) and 0.11 (95% CI 0.07, 0.16) respectively. Thus, increase mean motor and cognitive scores was observed with decrease in the severity of stunting at specified time-point as well as with age of children. These measures were adjusted maternal education, BMI z-scores of children, initiation of complementary feeding along with wave of enrollment, and sub-district of origin.

Conclusions: Our analysis showed that lagged LAZ score was significantly associated with both motor and cognitive development during the first 24 mo of life. This association was highest when outcome is measured at 16 mo. Thus, reduction in the prevalence of stunting before 16 mo will have significant effect on motor as well as cognitive development during the first 24 mo of a child's life.

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CHAPTER I: LITERATURE REVIEW

Early childhood development is the attainment of gross motor, fine motor, and cognitive abilities including language or communication, problem-solving, and social skills (1). The gross motor skills are the use of large muscles to achieve sitting, crawling and walking in early life. The fine motor skills are the use of small muscles in the hands and fingers to perform tasks like picking up small objects and feeding. Cognitive development refers to how a child perceives, thinks, and gains an understanding of his or her world and includes remembering, problem-solving, and decision-making. Language or communication skills is the ability to understand others and to express oneself, both verbal and nonverbal. Social skills are the child's interactions with their family and other children (2). The human brain develops through neurogenesis, axonal and dendritic growth, synaptogenesis, cell death, synaptic pruning, myelination, and gliogenesis (3). The brain grows more rapidly after conception and during the first three years of life than other times (1,2,3). Advances in brain science have documented that the origins of adult health and well-being are grounded in early childhood, from conception through the age of 24 months (mo) (5). Developmental delays are apparent among children before 12 mo, and these delays worsen during early childhood (6).

An estimated 80.8 million children (36.8%) of three and four-year-olds across 35 low and middle-income countries (LMICs) do not attain basic cognitive and socio-emotional skills (7). There are an estimated 219 million children (almost 39% less than five years of age) in low-income and middle-income countries who are at risk of not reaching their developmental potential (7,15).

Linear growth failure is pronounced in the first 12–18 mo of child age (8). Stunting before the age of 24 mo is particularly problematic as it is related to poor child development (5).

Stunting is defined as when a child's length or height is below negative two standard deviations (SDs) from World Health Organization (WHO)'s child growth Standards median for the same age and sex (9,10). Stunted growth is one of the critical risk factors that prevent children from reaching their developmental potential (11). Globally, there are an estimated 150 million under-five children who are stunted (16).

Each unit increase in length-for-age z score (LAZ) was associated with higher (+0.24-SD) increase in cognitive score among children less than 24 mo compared to children greater than 24 mo (+0.09 SD) (12). Studies from low-income and middle-income countries indicate that the first 24 mo after birth (13,14) is the most crucial period when linear growth is associated with later cognition, executive function, and school attainment. This association is weakened after 24 mo (12,14). Studies which examined the effect of macronutrient supplementation indicated the importance of the first 24 mo for intellectual development (15). Improvements in height-for-age might occur after 24 mo, but associations with cognitive gains remain uncertain (6,12,13, 15,16). As stunting-attributable developmental deficits among children, less than 24 mo of age has considerable consequences at the population-level, this has been identified as an ongoing priority area of global research (under the thematic goal of "Advance identification of risk factors, and a better understanding of the burden") (17). Thus, the initial 24 mo of life is a crucial period to quantify the association between linear growth and cognitive development to inform the development of evidence-based intervention programs.

Two meta-analyses and several cross-sectional studies provide initial evidence on the link between impaired linear growth and child development (11,12,16,17). In addition, the analysis of longitudinal data from prospective cohorts from Guatemala, Philippines, Jamaica, Peru, Kenya, Indonesia, Brazil, and South Africa, showed the

association of stunting between 12 and 36 mo of age with lower school grades in middle childhood (20, 23, 24, 26, 27). Cebu Longitudinal Health and Nutrition Survey from the Philippines showed that for every increase of one Z-score in linear growth, cognitive ability increased by approximately 0.08 standard deviation ($P < 0.001$) among children of 11 years of age (24). The study by Berkman DS *et al.* among Peruvian children between 12 and 24 mo of age reported the association of severe growth retardation ($LAZ \leq 3$ SD) with a ten-point deficit in Intelligence quotient (IQ) at nine years of age (19). A meta-analysis of studies from 29 low and middle-income countries showed each unit increase in LAZ for children less than 24 mo of age was associated with a +0.22-SD (95% CI, 0.17-0.27) increase in cognition at 5 to 11 years (12). In South Asia, the study found that cognitive development was negatively associated with stunting (OR = 0.72, 95% CI [0.60, 0.86]) among children aged 36-59 mo (29). Further, the systematic review and meta-analysis of more than 20 studies of nutrition interventions in low and middle-income countries (LMICs) found an association of stunting among children under two years with cognitive development at follow up within a year (20,21). Collectively, these prospective cohort studies consistently showed significant associations between stunting by the age of 24 or 36 mo and later cognitive deficits, and school achievement (19,22–25). However, only one recent study showed no significant relationship between stunting and poor school progress (28).

Among children aged less than 24 mo, an association of length-for-age z score (LAZ) at 6 mo with cognition (language) was 0.13 ± 0.02 SD and rate of change of LAZ from 6 to 18 mo was 0.11 ± 0.03 SD (27). The odds of stunting for low Bayley cognitive scores at 9 and 24 mo ranged from 2.0-2.9 ($p < 0.05$) (28). Moreover, lower LAZ at 4 and 12 mo were associated with lower cognitive function scores at 24 mo ($p \leq 0.03$) (33). Furthermore, the study among children in Burkina Faso, Ghana, and

Malawi showed that for the motor score, an estimate of the association of length-for-age z score (LAZ) at 6 mo was 0.16 ± 0.02 SD and the rate of change of LAZ from 6 to 18 mo was 0.22 ± 0.03 SD. The odds of stunting for low Bayley motor scores at 9 and 24 mo ranged from 1.8 to 3.3 ($p < 0.05$) (27). Also, stunting increased the odds of not standing alone at 11 mo and not walking alone at 18 mo by 9.7 and 6.1, respectively (29). However, the Kenyan study showed that height is not related to motor development at 6 mo of age (30). Collectively, these demonstrate there is an association between LAZ and both cognition and motor scores among children less than 24 mo; however, this association remains to be uncertain and linearly quantified.

Studies suggest various mechanistic pathways from stunting to poor cognitive development including neurological (31), infectious disease-related (11,13) and hormonal (32). A study by Chandy C *et al.* proposed three mechanisms linking early stunting to early childhood development. These include: (a) biological insults that disrupt early brain development, (b) delayed motor skills that may disrupt the exploration associated with cognitive development, and (c) reduced expectations from parents and peers, based on short stature (31). Thus, stunted children are continually under nutritional stress and prone to infections including higher incidence of diarrhea leading to poor cognitive development (33,34).

The timing of stunting assessment appears to be critical. During the early ages of undernutrition (nutritional insults), notable recovery of height (known as catch-up growth) is often possible with interventions. Generally, the earlier the interventions, the larger the benefit (35,36). The timing of catch-up growth before five years of age is unknown and can occur within the first two years of life (37). Further, a study from Guatemala showed that growth and development were related up to age 24 mo but not from 24 to 36 mo (38).

We found that most of the current literature is focused on cognitive development among children greater than two years of age. Furthermore, the association between linear growth and cognitive or motor development among children less than two years remains to be uncertain and linearly quantified. Due to this gap in the literature, we aim to evaluate the association between linear growth (retardation) and motor skills as well as cognitive development among children less than 24 mo of age. To best of our knowledge, currently, there has been no prospective cohort study of cognitive development at less than two years of age in Bangladesh, which low-income settings with a high prevalence of poor nutrition and enteric diseases.

Further, stunting levels in South Asia are very high, particularly Bangladesh (prevalence is estimated to be 36%) (17). Bangladesh is among the top thirty countries in terms of the prevalence of stunting in children less than five years of age (17). Considering the implication on public health policy, it is essential to know the association between stunting and cognition among children less than 24 mo in Bangladesh.

The researchers from Emory University and CARE-USA conducted a prospective cohort study to evaluate the impact of a nutrition intervention in a low socio-economic setting in Bangladesh. We used the data from this impact evaluation to study the association between linear growth (and stunting) at the ages of 3, 9 and 16 mo with motor development at the ages of 9, 16, and 24 mo as well as cognitive development at 16 and 24 mo.

CHAPTER II: MANUSCRIPT

Linear growth and child development during early childhood in Bangladesh

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Abstract:

Introduction: We assessed the longitudinal relationships between length and motor, and cognitive development among children less than 24 mo in rural Bangladesh.

Design: Prospective longitudinal cohort study with structured home interviews during pregnancy and 3, 9, 16 and 24 mo after delivery.

Setting: Two rural sub-districts (Karimganj; Katiadi) of Kishoreganj district, Bangladesh.

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Results: We observed decrease in mean length-for-age Z (LAZ) scores from -1.1 at 3 mo to -2.3 at 24 mo. Similar trend was observed in head circumference z-scores (HCZ) although BMI z-scores (BMIZ) remained constant between 3 to 24 mo. For one unit increase in LAZ score at 3 mo, the motor z-score at 9 mo increased by 0.10 (95% CI 0.07, 0.14). Similarly, one unit change in LAZ score at 9 mo and 16 mo was associated with increase in motor z-scores at 16 mo and 24 mo by 0.16 (95% CI 0.12, 0.20) and 0.12 (95% CI 0.08, 0.16) respectively. Additionally, for one unit increase in LAZ score at 9 and 16 mo, the cognitive z-score at 16 and 24 mo was increased by 0.12 (95% CI 0.08, 0.16) and 0.11 (95% CI 0.07, 0.16) respectively. Thus, increase mean motor and cognitive scores was observed with decrease in the severity of stunting at specified time-point as well as with age of children. These measures were adjusted maternal education, BMI z-scores of children, initiation of complementary feeding along with wave of enrollment, and sub-district of origin.

Conclusions: Our analysis showed that lagged LAZ score was significantly associated with both motor and cognitive development during the first 24 mo of life. This association was highest when outcome is measured at 16 mo. Thus, reduction in the prevalence of stunting before 16 mo will have significant effect on motor as well as cognitive development during the first 24 mo of a child's life.

Introduction:

Developmental delays are apparent among children before 12 mo, and these delays worsen during early childhood (6). There are an estimated 219 million children (almost 39% less than five years of age) in low-income and middle-income countries who are at risk of not reaching their developmental potential (7,15). An estimated 80.8 million children (36.8%) of three and four-year-olds across 35 low and middle-income countries (LMICs) do not attain basic cognitive and socio-emotional skills (7).

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Previous studies from low-income and middle-income countries consistently showed significant associations between stunting by the age of 24 or 36 mo and later cognitive deficits, and school achievement (19,22–25). As stunting-attributable developmental deficits among children, less than 24 mo of age has considerable consequences at the population-level, this has been identified as an ongoing priority area of global research (under the thematic goal of “Advance identification of risk factors, and a better understanding of the burden”) (17). Studies among children aged less than 24 mo demonstrate there is an association between LAZ and both cognition, and motor scores; however, this association remains to be uncertain and linearly quantified (27,28,29,30).

Studies suggest various mechanistic pathways from stunting to poor cognitive development including neurological (31), infectious disease-related (11,13) and

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The researchers from Emory University and CARE-USA conducted a prospective cohort study to evaluate the impact of a nutrition intervention in a low socio-economic setting in Bangladesh. We used the data from this impact evaluation to study the association between linear growth (and stunting) at the ages of 3, 9 and 16 mo with motor development at the ages of 9, 16, and 24 mo as well as cognitive development at 16 and 24 mo.

Methods:

The original intervention:

CARE, USA implemented a community-based Infant and Young Child Feeding (IYCF) program in Bangladesh. The program was known in Bengali as “Akhoni Shomay”- Window of Opportunity. The intervention area was Karimganj, a rural sub-district of Kishoreganj, where pregnant women and mothers with newborns were eligible to voluntarily participate in behavior change communication activities and receive multiple micronutrient supplementation. A non-adjacent sub-district (Katiadi) in the same district (Kishoreganj) served as a control. Previously published articles described the details of the cohort, program and data collection instruments (39–41).

International Centre for Diarrheal Disease Research, Bangladesh (ICDDR, B) approved the original study protocol. Researchers received a waiver from

Emory IRB review after determining that researchers are not “engaged” in research with human subjects.

Recruitment of the cohort and timing of assessments:

The cohort enrolled 1200 pregnant women between January 2011 to January 2014 from Karimganj. An equal number of pregnant women were enrolled from Katiadi. Pregnant women were recruited in their seventh month of gestation, with follow-up of their offspring scheduled at 3, 9, 16, and 24 mo of age. The first wave of participants was recruited in January and February 2011, the second was recruited in May, and June 2011, and the third and final wave was enrolled in September and October 2011.

Measurement of length:

The length of the child was measured at the ages of 3, 9, 16 and 24 mo follow-up by trained study personnel using methods prescribed by WHO (39). The length measurements were recorded in duplicate, with the average used in analyses.

Measurement of development:

There were two primary outcome measures in this study: child motor development and child cognitive development. Child motor development was assessed at the ages of 9, 16 and 24 mo and cognitive development was assessed at 16 and 24 mo. The motor skills at the age of 9 mo were assessed using the WHO motor development standards (40). The WHO motor development standards evaluate acquisition of key gross motor skills (which are fundamental to self-sufficient erect locomotion) through six milestones: sitting, crawling, standing without help, standing with help, walking without help, and walking with help.

Furthermore, motor and cognitive development were assessed at the age of 16 mo using Ages and Stages Questionnaire (ASQ-3) (41), and at the age of 24 mo using CDC's developmental milestones screening checklist (42). Ages and Stages Questionnaire, third edition (ASQ-3, 2009) evaluates communication, gross motor, fine motor, problem-solving, and personal-social skills (41). Similar to ASQ-3, CDC's developmental milestones screening checklist evaluates communication, social/emotional skills, problem-solving, and physical development. We calculated index (composite) scores across all scales.

Measurement of other variables:

Birth order was estimated from the number of total births at the time of recruitment of pregnant women. Only singleton births were considered. At each eligible visit weight, length and head circumference of children were measured using standard procedures. Body mass index (BMI) of children was calculated as kg/m². BMI and head circumference (HC) were converted to z scores with the use of the age-appropriate WHO reference (42). Initiation of complementary feeding (CF) at the infant age of less than 6 mo (expressed as yes/no) was estimated from variables- 'time when an infant was first given- any liquid', 'water' and 'solid/semi-solid.' Other covariates considered for analysis were maternal age, education, and height, counseling during pregnancy, a wave of the cohort, exclusive breastfeeding till 3 mo, sex and head circumference of the child.

Data manipulation:

The length was converted to z scores with the use of the age-appropriate WHO reference (41,42). We used WHO's SAS igrowup package for calculation of Length-for-age Z-scores (LAZs) (43). We used the LAZ scores as the primary exposure for the

study. Given the longitudinal nature of the data, a lag in LAZ score (by 6-8 mo) was built into our analyses in which the outcome measures (cognitive development and motor skills) were compared to the LAZ scores at previous measurement time-point. As a result, LAZ at 24 mo was dropped as it was not needed.

Furthermore, the motor and cognitive index scores were standardized using internal mean and standard deviation (refer to Table 2). The use of standardized scores permits comparison of a child's motor and cognitive performance over time within as well as across children.

Using the WHO guideline of extreme LAZ scores, we decided to exclude the observations with LAZ scores below -6 or more than 6 (42). These observations could be due to measurement error and cause potential bias. There were 34 such observations across all time-points. As mentioned earlier, we also excluded LAZ scores at 24 mo of age; thus, only LAZ scores at the ages of 3, 9, and 16 mo were considered for analysis.

Statistical analysis:

Descriptive:

Maternal height, child Length, BMI, and head circumference, Motor and cognitive index scores, were treated as continuous variables. Child sex, birth order, exclusive breastfeeding at 3 mo, initiation of complementary feeding before 6 mo, maternal education, and age, sub-district origin, and enrollment wave were treated as categorical variables. Maternal age was categorized as <20 y, 20-24 y, 25-29 y, 30-34 y, and ≥ 35 y. Based on the number of years of education, maternal education was categorized into four groups (No formal education, Primary (1-5 y), Secondary (6-13 y), and Higher (>13 y)). Descriptive data are summarized in Tables 1 and 2. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as column percentages while showing only relevant categories.

Model building:

LAZ scores were used as indicator of size and changes in Z-scores over time as indicator of growth. We assessed associations between LAZ scores at specified times (3, 9, and 16 mo) and child development at the next measurement times (9, 16, and 24 mo). We examined the following relationships: 1) LAZ score as a predictor of the motor z-score and 2) LAZ score as a predictor of the cognitive z-score. The Pearson correlation coefficient between outcome measures at different time-points was calculated. We also randomly sampled 100 individuals and looked at trajectories for average change in motor as well as cognitive z-scores (at each time-point) over lagged length-for-age z-scores. Considering the outcome measures were forced to not change on average over time and weak correlation between them across different time-points (Tables 3B and 3C), we used linear models for analysis.

All analyses were conducted in SAS (Version 9.4, SAS Institute, Cary, NC) software. The SAS 'proc glm' procedure was used for multivariable linear regression analysis. The level of significance for statistical tests was set to $p < 0.05$. Based on the previous studies and logical sequence of events, we considered all potential covariates in a full model. We arrived at a final model with the use of backward elimination. We did separate modeling each for our two outcomes of interest: motor and cognition z-scores. To check the fitness of the model, we conducted likelihood ratio tests comparing full and reduced (final) models.

Exploratory analyses:

Through plotting of observed data, we tried to explore the relationship between mean motor Z-scores at the age of 9, 16, and 24 mo and three different levels of LAZ scores at the ages 3, 9, and 16 mo, respectively (**Figure 2**). Based on WHO standards, the LAZ scores were categorized into three levels as < -3 (severe stunting), between $\geq -$

3 and < -2 (moderate stunting) and ≥ -2 LAZ (no stunting) (43). We also plotted mean cognitive z-score at 16 and 24 mo against different levels of LAZ scores (as mentioned above) at 9 and 16 mo, respectively (**Figure 3**). With the use of the final model, we estimated mean motor and cognitive Z-score at three different LAZs (< -3 , ≥ -3 and < -2 , ≥ -2) using the final reduced model. We also estimated the difference in mean motor and cognitive Z-scores between no stunting and other categories. All analyses were adjusted for the selected child characteristics (sex, BMIZ, birth order, exclusive breastfeeding (EBF), and initiation of complementary feeding (CF)) and maternal characteristics (counseling during pregnancy, age, height, and education). We also adjusted for sub-district of origin and cohort enrollment wave to control for possible intervention and enrollment wave-specific fixed effects, respectively.

Results:

Out of the 2400 women recruited, we completed follow-up from 2011 to 2014, of 2192, 2074, 1969, and 1885 mother-child dyads at 3, 9, 16, and 24 mo of infant age, respectively (**Figure 1**). Attrition rates did not differ between the two sub-districts. Maternal age, height, education, and counseling during pregnancy were similar across the two sub-districts. The distribution of infant sex, birth order, initiation of complementary feeding before six months, infant length, Body Mass Index (BMI) and head circumference at 3, 9, 16 and 24 mo were similar in both the intervention and control group. However, a higher proportion of infants received exclusive breastfeeding until three mo in the intervention sub-district (**Table 1**).

We observed a decrease in mean LAZ scores from -1.1 at 3 mo to -2.3 at 24 mo. Similarly, the head-circumference-for-age z-score dropped from -0.6 to -1.5 between same period. However, BMI-for-age z-score remained constant at -0.5 between 3 to 24

mo except for 16 mo (-0.6) (**Table 2**). Mean motor development index scores were similar across the intervention and control groups at each time point. However, the mean cognitive development index scores were higher in the intervention sub-district. This difference was lost by age 24 mo.

We computed a Pearson correlation coefficient to assess the relationship between LAZ scores at different time-points (**Table 3A**). The LAZ scores at 3 mo had moderate positive correlation with LAZ scores at 9, 16 and 24 mo [$r = 0.64$ ($p < 0.01$), 0.60 ($p < 0.01$), 0.57 ($p < 0.01$), respectively]. However, LAZ scores at 9 mo had strong positive correlation with LAZ scores at 16 and 24 mo, respectively [$r = 0.84$ ($p < 0.01$), 0.80 ($p < 0.01$)]. Similarly, strong positive correlation was observed between LAZ at 16 mo and 24 mo [$r = 0.88$ ($p < 0.01$)]. Thus, we observed with an increase in age, there was an increase in the correlation between LAZ scores measured at subsequent time-points. Further, we calculated the correlation within 9, 16 and 24 mo of motor z-scores (**Table 3B**) as well as 16 and 24 mo of cognitive z scores. Within each time-point, we observed weak positive correlations for both outcomes [where all $r < 0.30$, ($p < 0.01$)].

Table 4A represents the multivariable regression coefficients for the association between motor z-scores at 9, 16 and 24 mo and lagged LAZ scores at 3, 9 and 16 mo, respectively, adjusted for intervention, enrollment wave, Body Mass Index (BMI) z-scores, initiation of complementary feeding before 6 mo, maternal education. For each unit increase of LAZ score at 3 mo, the motor z-score at 9 mo increased by 0.10 (95% CI 0.07, 0.14). Furthermore, one unit change in LAZ score at 9 mo and 16 mo was associated with the increase in motor z-scores at 16 mo and 24 mo by 0.16 (95% CI 0.12, 0.20) and 0.12 (95% CI 0.08, 0.16) respectively. Similarly, an association was found between BMI z-scores and motor z-scores at all time-points. However, this association decreased consistently from 9 to 24 mo (0.11 to 0.07). The motor z-scores

at 9 and 24 mo among children in intervention group was 0.13 ($p<0.01$) and 0.95 ($p<0.01$) higher compared to control group, respectively. The initiation of the complementary feeding after 6 mo (compared to < 6 mo) was associated with 0.12 ($p<0.01$) increase in motor z-score at 9 mo. However, this relationship weakened at 16 and 24 mo. Motor z-scores at all timepoints were higher if child's mother has secondary level of education compared to no education. The coefficient with adjustment of some additional variables presented as supplementary tables (Table 6A). While results of parsimonious model presented here.

Table 4B presents the multivariable regression coefficients for the association between cognitive z-scores at ages 16 and 24 mo and LAZ scores at ages 9 and 16 mo, respectively, adjusted for intervention, BMI z-scores, and maternal education. For one unit increase in LAZ score at 9 and 16 mo, the cognitive z-score at 16 and 24 mo was increased by 0.12 (95% CI 0.08, 0.16) and 0.11 (95% CI 0.07, 0.16) respectively. Like motor z-scores, the association between BMI z-scores and cognitive z-scores reduced from 16 to 24 mo. Thus, BMI z-score is a significant predictor of cognitive z-score at 16 mo but not at 24 mo. The average cognitive z score at 16 and 24 mo among children in intervention group was 0.12 ($p<0.01$) and 0.30 ($p<0.01$), respectively, higher than control group. Children achieved higher cognitive z scores, as maternal education changed from primary to higher level. The coefficient with adjustment of some additional variables presented as supplementary tables (Table 6B). While results of parsimonious model presented here.

Furthermore, we observed with a decrease in severity of stunting (i.e. increase in LAZ scores) at the age of 3, 9, and 16 mo, there was a rise in the mean motor Z-scores at the age of 9, 16, and 24 mo, respectively. (**Figure 2**). We observed a similar trend between the LAZ scores at ages 9 and 16 mo and the mean cognition z-scores at

ages 16 and 24 mo, respectively (**Figure 3**). Using final models, we estimated average motor and cognitive z-scores at different levels of stunting (**Table 5**). An estimated motor z-score at 9, 16 and 24 mo for non-stunted children was 0.06 (+/- 0.10), 0.10 (+/- 0.10), and 0.54 (+/- 0.10) respectively. As there was a decrease in LAZ score (i.e. increased in severity of stunting), the significant decline in mean motor z-score was observed. The difference in mean motor z-score between non-stunted children and moderately or severely stunted children was highest at 9 mo. This difference gradually reduced from 9 to 24 mo. An estimated cognitive z-score at 16 and 24 mo for non-stunted children was 0.26 (+/- 0.07) and 0.27 (+/- 0.08) respectively. With the increase in the severity of stunting, a significant decline in cognitive z-score was observed. The difference in mean cognitive z-scores between non-stunted and moderately or severely stunted children decreased over time.

Discussion:

The objective of this study was to examine the association between LAZ score and the motor and cognitive z-scores in a cohort of Bangladeshi children. Our analysis found that LAZ score was significantly associated with both motor and cognitive development during the first 2 years of life, among children in Bangladesh. With the increase in LAZ score, the significant increase in a motor as well as cognitive z-scores was observed. These findings corroborate the findings of other studies conducted in other regions (27,28). In addition, head circumference z-score was not a significant predictor of the motor or cognitive z-scores (data not shown). Previous studies showed a stronger association between LAZ score and motor development compared to an association between LAZ score and cognitive development (38). However, as per our analysis, we found the association between LAZ scores and motor development to not

be meaningfully different from the association between LAZ score and cognitive development.

Strengths and limitations:

There are several strengths and limitations to this study. The standardized outcome measures over time are not strongly correlated. Also, these outcome measures were linearly changing with LAZ scores, so we could use the linear models. This allowed us to study the association between LAZ scores and cognitive or motor development at each specified time-point. Further, in our analyses, we lagged the LAZ scores to the previous measurement time points. Hence, our exposure was able to precede the outcome and associations were assessed prospectively. Unlike some previous studies which used WAZ scores, we used the BMIZ score which is also an indicator of undernutrition (26,38). Along with LAZ score, BMIZ score was also a significant predictor of both motor and cognitive development even after adjusting for covariates (Tables 4A and 4B). In addition to the prospective study design, another strength of this study was that we excluded very few observations based on extreme values of LAZ (<-6 and > +6). We anticipate our results are minimally impacted by measurement error. This study benefited from a large sample size of children under the age of two and the use of a standardized general developmental screening tool, the Age and Stages Questionnaire (ASQ) scale. The ASQ is cost-effective and could be completed within 12-18 minutes with a test-retest reliability of 92%, sensitivity of 87.4% and specificity of 95.7% (37). Moreover, validity has been examined across different cultures and communities across the world (37).

One limitation of this study was that by 24 mo, almost 500 mother-infant dyads were lost to follow up. The reason for this loss to follow up was either maternal or infant

death, out-migration, or refusal to participate. While this is high attrition, we expect that the loss to follow up due to maternal or infant deaths may have had worse outcomes than those retained in the study, which would, in fact, increase the strength of the association in our findings. Additionally, loss to follow up due to out-migration was random and hence will not lead to selection bias. However, the potential for selection bias from loss to follow-up due to refusal cannot be ruled out.

Multiple mechanistic pathways linking linear growth retardation and motor, or cognitive development have been proposed. First, it is hypothesized that a smaller body size affects motor activity, which would limit the child's ability to access stimulation (12, 42) and reduce opportunities for cognitive development (21). The second mechanism is the "Rosenthal Effect"- where a child's short stature lowers the caregivers' expectations about the child's developmental potential, hence reducing stimulation and the prospect of cognitive development(45). In contrast a study suggests linear growth retardation as not part of the mechanistic path leading to delayed cognitive and motor development (20) Thus, linear growth retardation and child development are not likely causally related but associated through a set of shared determinants (undernutrition, inadequate care, and repeated infections) (45).

Furthermore, a child's motor, psychosocial, and cognitive development occur interactively and dynamically with significant influence from their social environments (46). The lack of focus of the present study on mechanistic assessment prohibits a definitive framework for pathways and mediators of motor and cognitive development among young children. Expanding upon this current work, future studies should focus on identifying a definitive pathway linking linear growth (retardation) to the motor or cognitive development.

In conclusion, length is a significant predictor of both motor and cognitive development during the first 24 mo of a child's life. This association is highest at 16 months. Additionally, difference in motor development among non-stunted and moderately or severely stunted children gradually reduce with the age of children. More evidence from developing countries will help explain the underlying mechanisms and identify appropriate interventions to prevent neurodevelopmental delay in early childhood.

TABLES

Table 1. Characteristics of Infants and Mothers

| | Overall | | Intervention | | | Control |
|---|----------------|---------------|----------------|----------------|----------------|----------------|
| | Total | Total | Wave 1 | Wave 2 | Wave 3 | Total |
| Maternal Characteristics | | | | | | |
| Height, centimeter ¹ | 149.7 (5.4) | 150 (5.5) | 149.5 (5.9) | 150.1 (5.4) | 150.6 (5.2) | 149.3 (5.3) |
| Maternal age, years ² | | | | | | |
| <20 | 19.3 | 15.5 | 11.0 | 20.3 | 15.3 | 23.0 |
| 20-24 | 33.6 | 34.9 | 35.8 | 34.5 | 34.5 | 32.3 |
| 25-29 | 26.8 | 27.2 | 27.0 | 25.5 | 29.0 | 26.3 |
| 30-34 | 14.2 | 15.6 | 18.0 | 15.5 | 13.3 | 12.8 |
| >=35 | 6.1 | 6.8 | 8.3 | 4.3 | 8.0 | 5.6 |
| Education ² | | | | | | |
| No Education | 24.5 | 25.5 | 32.3 | 22.5 | 21.8 | 23.5 |
| Primary | 36.4 | 40.0 | 36.8 | 45.3 | 38.0 | 32.8 |
| Secondary | 30.0 | 25.1 | 22.0 | 24.0 | 29.3 | 34.9 |
| Higher | 0.6 | 0.3 | 0.0 | 0.5 | 0.5 | 0.9 |
| Missing | 8.5 | 9.1 | 9.0 | 7.8 | 10.5 | 7.9 |
| Counseling during Pregnancy ² | 62.0 | 61.8 | 47.0 | 61.5 | 76.8 | 62.3 |
| Infants' Characteristics | | | | | | |
| Sex ² Female | 50.3 | 50.5 | 50.0 | 52.3 | 49.0 | 50.1 |
| Birth Order ² | | | | | | |
| 1 | 27.0 | 26.7 | 23.6 | 29.4 | 26.9 | 27.3 |
| 2 | 24.2 | 25.2 | 24.5 | 25.1 | 26.1 | 23.1 |
| >=3 | 48.9 | 48.2 | 51.9 | 45.5 | 47.1 | 49.5 |
| Length at ¹ | | | | | | |
| 3 months | 57.9 (2.5) | 57.8 (2.4) | 58.1 (2.2) | 57.5 (2.4) | 57.9 (2.6) | 58.0 (2.4) |
| 9 months | 67.2 (2.9) | 67.1 (3.0) | 66.9 (2.7) | 66.9 (3.4) | 67.6 (2.7) | 67.1 (2.7) |
| 16 Months | 73.8 (3.1) | 73.8 (3.0) | 73.7 (2.8) | 73.6 (3.0) | 74.1 (3.1) | 73.8 (3.1) |
| 24 Months | 80.0 (3.4) | 80.0 (3.5) | 79.6 (3.2) | 80.1 (3.8) | 80.3 (3.4) | 79.9 (3.3) |
| BMI at ¹ | | | | | | |
| 3 months | 15.9 (1.7) | 15.9 (1.6) | 15.9 (1.7) | 16.0 (1.7) | 15.9 (1.5) | 15.8 (1.7) |
| 9 months | 16.2 (3.3) | 16.3 (4.1) | 16.4 (1.7) | 16.2 (6.6) | 16.2 (1.5) | 16.2 (2.3) |
| 16 Months | 15.4 (1.5) | 15.4 (1.3) | 15.3 (1.3) | 15.4 (1.2) | 15.6 (1.3) | 15.5 (1.7) |
| 24 Months | 15.1 (1.4) | 15.1 (1.5) | 15.4 (1.4) | 15.0 (1.8) | 15.0 (1.2) | 15.0 (1.4) |

Table 1. Characteristics of Infants and Mothers

| | Overall | | Intervention | | | Control |
|---------------------------------|----------------|---------------|---------------------|---------------|---------------|----------------|
| | Total | Total | Wave 1 | Wave 2 | Wave 3 | Total |
| Head Circumference ¹ | | | | | | |
| 3 months | 39.1 (1.4) | 39.1 (1.4) | 39.2 (1.4) | 39.0 (1.4) | 39.0 (1.4) | 39.1 (1.4) |
| 9 months | 42.9 (1.4) | 42.9 (1.5) | 42.7 (1.4) | 42.8 (1.4) | 43.0 (1.5) | 42.8 (1.4) |
| 16 Months | 44.6 (1.4) | 44.6 (1.4) | 44.7 (1.4) | 44.5 (1.3) | 44.6 (1.5) | 44.5 (1.4) |
| 24 Months | 45.7 (1.7) | 45.6 (1.4) | 45.7 (1.4) | 45.6 (1.4) | 45.7 (1.5) | 45.7 (1.9) |
| EBF at 3 months ² | 21.8 | 33.8 | 36.0 | 38.7 | 26.6 | 9.9 |
| CFI > 6 months ² | 18.1 | 15.3 | 14.5 | 14.8 | 16.7 | 21.0 |

¹ Mean (SD) ² Percentage

Table 2. Length for age Z scores and measure of physical and cognitive development

| | Overall | | Intervention | | Control | |
|---|---------|------|--------------|------|---------|------|
| | Mean | SD | Mean | SD | Mean | SD |
| Length-for-age Z score | | | | | | |
| 3 months | -1.1 | 1.2 | -1.0 | 1.2 | -1.1 | 1.2 |
| 9 months | -1.7 | 1.1 | -1.6 | 1.0 | -1.7 | 1.1 |
| 16 months | -2.2 | 1.0 | -2.2 | 1.0 | -2.3 | 1.1 |
| 24 months | -2.3 | 1.0 | -2.3 | 1.0 | -2.3 | 1.0 |
| BMI-for-age Z score | | | | | | |
| 3 months | -0.5 | 1.1 | -0.4 | 1.1 | -0.5 | 1.2 |
| 9 months | -0.5 | 1.1 | -0.5 | 1.0 | -0.6 | 1.1 |
| 16 months | -0.6 | 1.0 | -0.5 | 0.9 | -0.6 | 1.0 |
| 24 months | -0.5 | 1.0 | -0.4 | 0.9 | -0.5 | 1.0 |
| Head Circumference-for-age Z score | | | | | | |
| 3 months | -0.6 | 1.1 | -0.5 | 1.1 | -0.6 | 1.1 |
| 9 months | -1.2 | 1.0 | -1.2 | 1.0 | -1.2 | 0.9 |
| 16 months | -1.4 | 0.9 | -1.4 | 0.9 | -1.5 | 0.9 |
| 24 months | -1.5 | 0.9 | -1.5 | 0.9 | -1.5 | 0.9 |
| Motor Development Index scores ^a | | | | | | |
| 9 months | 3.4 | 1.0 | 3.5 | 0.9 | 3.4 | 1.0 |
| 16 months | 80.0 | 25.3 | 79.4 | 24.4 | 80.7 | 26.0 |
| 24 months | 4.5 | 0.8 | 4.8 | 0.5 | 4.1 | 0.8 |
| Cognitive Development Index scores ^a | | | | | | |
| 16 months | 142.6 | 32.5 | 144.2 | 31.0 | 141.0 | 33.9 |
| 24 months | 16.2 | 1.6 | 16.5 | 1.7 | 16.0 | 1.6 |

^a WHO motor development six milestones at 9 months; Ages and Stages Questionnaire (ASQ-3) at 16 month & Composite score from CDC's Developmental Milestones for 2-year old

Note: 9-month motor score on a scale of 6, 16-month motor score on a scale of 120, 24-month motor score on a scale of 5; 16-month motor score on a scale of 189, 24-month motor score on a scale of 22

Table 3A: Pearson Correlation among length-for-age z-scores

| LAZ scores at | 3mo | 9 mo | 16 mo | 24 mo |
|---------------|------|------|-------|-------|
| 3 mo | - | | | |
| 9 mo | 0.64 | - | | |
| 16 mo | 0.60 | 0.84 | - | |
| 24 mo | 0.57 | 0.80 | 0.88 | - |

Table 3B: Pearson Correlation among motor z-scores

| Motor z scores at | 9 mo | 16 mo | 24 mo |
|-------------------|------|-------|-------|
| 9 mo | - | | |
| 16 mo | 0.29 | - | |
| 24 mo | 0.19 | 0.19 | - |

Table 3C: Pearson Correlation among cognitive z-scores

| Cognitive z-scores at | 16 mo | 24 mo |
|-----------------------|-------|-------|
| 16 mo | - | |
| 24 mo | 0.26 | - |

Table 4A: Results of linear models for motor development z-scores

| Parameter | Coeff at 9 mo | 95% CI | Coeff at 16 mo | 95% CI | Coeff at 24 mo | 95% CI |
|----------------------------|------------------|----------------|-------------------|-----------------|-------------------|------------------|
| Intercept | -0.06 | -0.17, 0.05 | 0.29 | 0.06, 0.43 | -0.22 | -0.36, - 0.08 |
| LAZ score | 0.10 | 0.07, 0.14 | 0.16 | 0.12, 0.20 | 0.12 | 0.08, 0.16 |
| Intervention | 0.13 | 0.05, 0.22 | -0.03 | -0.11, 0.06 | 0.95 | 0.87, 1.02 |
| Wave | | | | | | |
| Wave 1 | ref | | ref | | ref | |
| Wave 2 | -0.07 | -0.18, 0.03 | -0.21 | -0.31, -0.10 | 0.06 | -0.04, 0.16 |
| Wave 3 | 0.15 | 0.04, 0.25 | -0.25 | -0.35, -0.14 | -0.20 | -0.3, - 0.1 |
| BMIZ score | 0.11 | 0.08, 0.15 | 0.09 | 0.04, 0.13 | 0.07 | 0.03, 0.11 |
| Initiation of CF > 6 mo | 0.12 | 0.01, 0.23 | 0.05 | -0.06, 0.16 | 0.07 | -0.03, 0.17 |
| Maternal Education | | | | | | |
| No Education | ref | | ref | | ref | |
| Primary | 0.11 | 0.01, 0.22 | 0.16 | 0.05, 0.27 | 0.05 | -0.05, 0.15 |
| Secondary | 0.22 | 0.11, 0.33 | 0.37 | 0.25, 0.48 | 0.17 | 0.07, 0.28 |
| Higher | 0.15 | -0.38, 0.68 | 0.29 | -0.23, 0.82 | 0.16 | -0.34, 0.67 |

Note: LAZ score: length-for-age z-score; BMIZ score: BMI-for-age z-score; CF: Complementary Feeding; Coeff: Coefficient

Note: The LAZ scores were lagged at 3, 9 and 16 mo for calculation of coefficient at 9, 16 and 24 mo respectively

Table 4B: Results of linear models for cognitive development z-scores

| Parameter | Coefficient | | Coefficient | |
|--------------------|-------------|-------------|-------------|-------------|
| | at 16 mo | 95% CI | at 24 mo | 95% CI |
| Intercept | -0.05 | -0.17, 0.08 | 0.01 | -0.14, 0.16 |
| LAZ score | 0.12 | 0.08, 0.16 | 0.11 | 0.07, 0.16 |
| Intervention | 0.12 | 0.03, 0.20 | 0.3 | 0.21, 0.39 |
| BMIZ score | 0.10 | 0.06, 0.14 | 0.02 | -0.02, 0.07 |
| Maternal Education | | | | |
| No Education | ref | | ref | |
| Primary | 0.23 | 0.12, 0.34 | 0.1 | -0.01, 0.22 |
| Secondary | 0.43 | 0.32, 0.54 | 0.17 | 0.06, 0.29 |
| Higher | 0.52 | -0.01, 1.04 | 0.17 | -0.41, 0.75 |

Note: LAZ score: length-for-age z-score; BMIZ score: BMI-for-age z-score; CF: Complementary Feeding

Note: The LAZ scores were lagged at 9 and 16 mo for calculation of coefficient at 16 and 24 mo respectively

Table 5: An adjusted estimated measure of motor and cognitive development z-score

| Age | Stunting Status | Motor Score ¹ | | Diff | 95% CI | Cognitive Score ¹ | | Diff | 95% CI |
|-----------|-------------------|--------------------------|------|------|------------|------------------------------|------|------|------------|
| | | Mean | SE | | | Mean | SE | | |
| 9 months | No Stunting | 0.06 | 0.10 | ref | | - | - | - | - |
| | Moderate Stunting | -0.16 | 0.10 | 0.22 | 0.14, 0.30 | - | - | - | - |
| | Severe Stunting | -0.38 | 0.12 | 0.43 | 0.28, 0.59 | - | - | - | - |
| 16 months | No Stunting | 0.10 | 0.10 | ref | | 0.26 | 0.07 | ref | |
| | Moderate Stunting | -0.10 | 0.10 | 0.20 | 0.14, 0.27 | 0.09 | 0.08 | 0.17 | 0.10, 0.23 |
| | Severe Stunting | -0.31 | 0.11 | 0.41 | 0.28, 0.54 | -0.08 | 0.09 | 0.34 | 0.21, 0.46 |
| 24 months | No Stunting | 0.54 | 0.10 | ref | | 0.27 | 0.08 | ref | |
| | Moderate Stunting | 0.40 | 0.09 | 0.14 | 0.09, 0.19 | 0.15 | 0.08 | 0.11 | 0.05, 0.17 |
| | Severe Stunting | 0.26 | 0.10 | 0.28 | 0.18, 0.38 | 0.04 | 0.09 | 0.22 | 0.11, 0.34 |

Note: Severe Stunting : <-3 LAZ, Moderate Stunting: >= -3 and <-2 LAZ; No Stunting: >= -2 LAZ
Diff: Difference

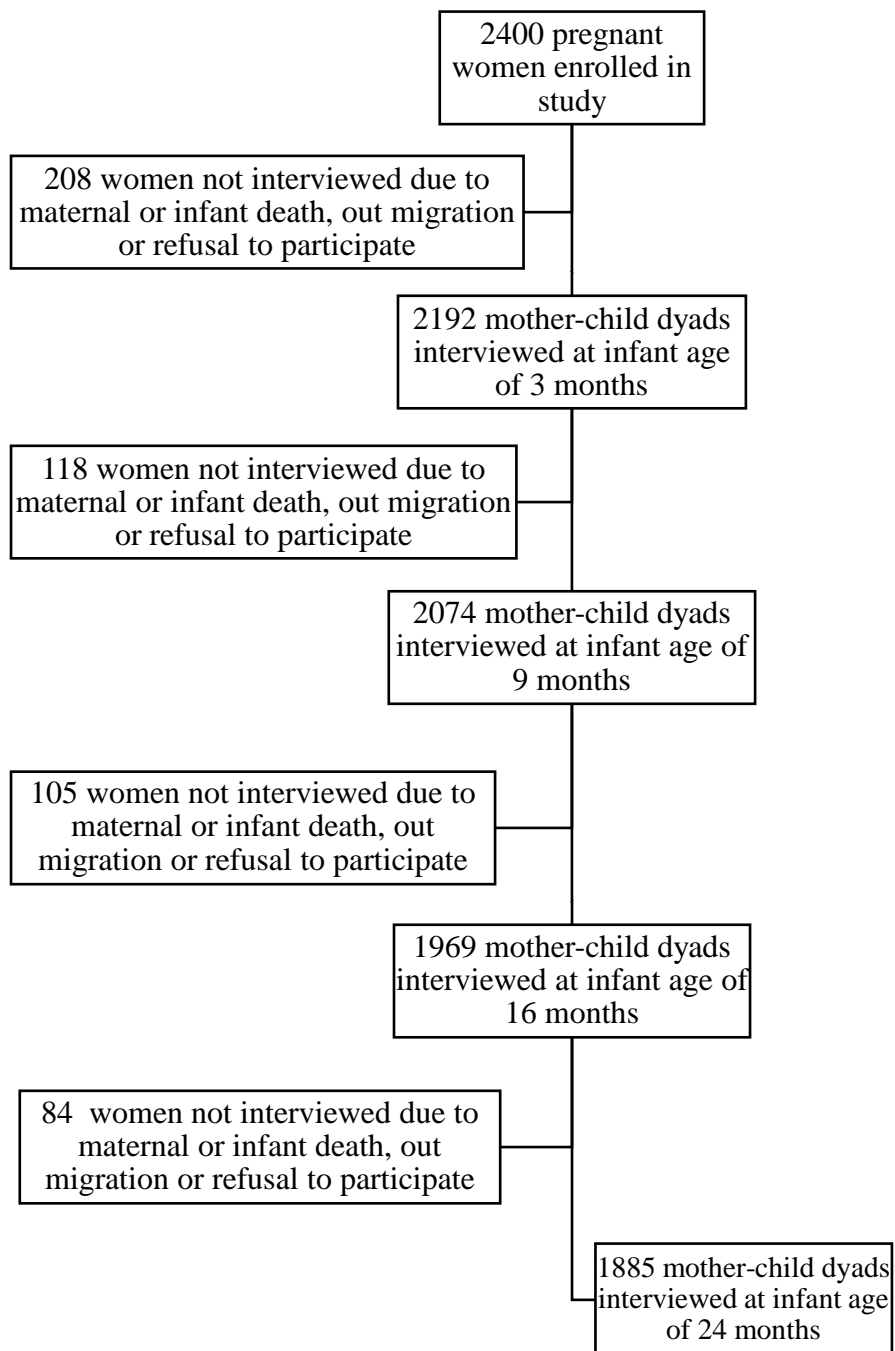
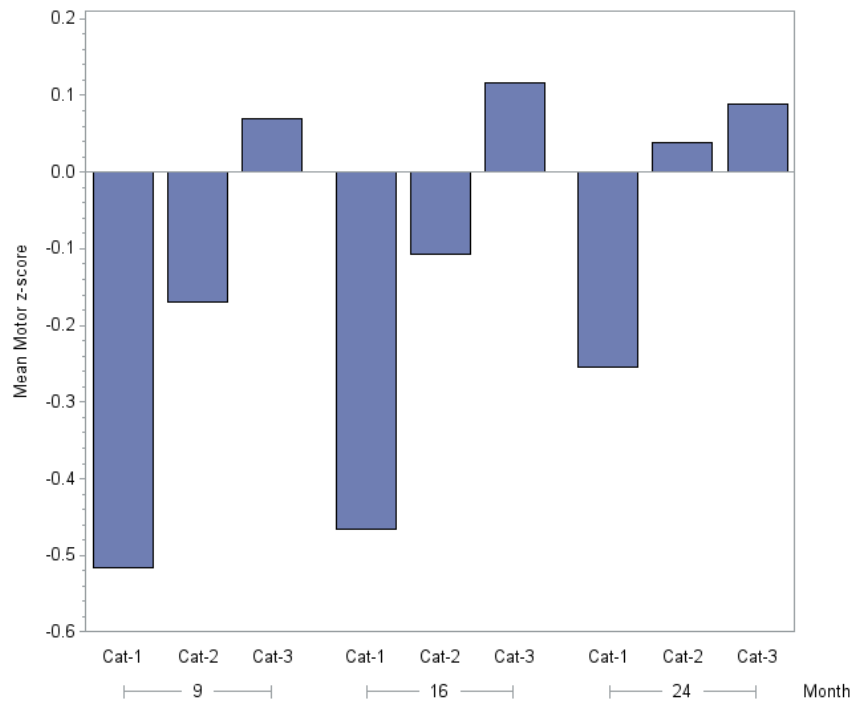
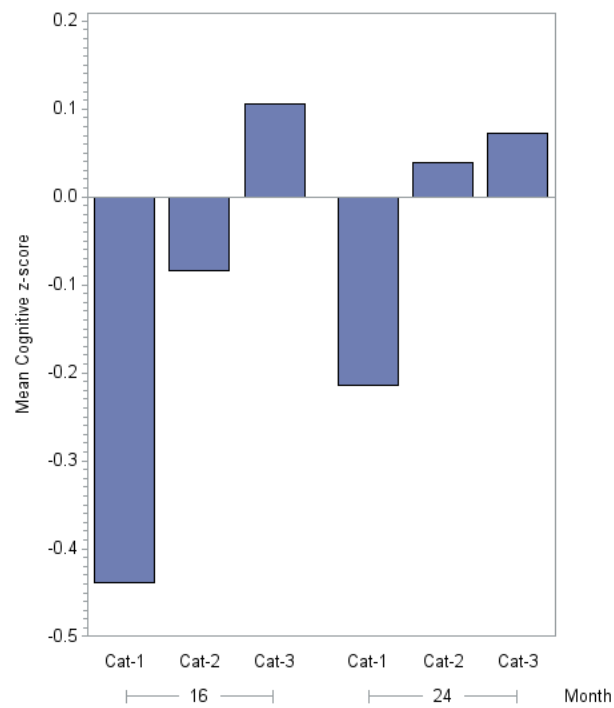
FIGURES**Figure 1:** Participant flow chart from January 2011 to January 2014

Figure 2: Mean motor z-score at 9, 16 and 24 months at different LAZ levels measured at previous timepoint (3, 9 & 16 months)



Note: Cat-1 is <-3 LAZ(Severe Stunting); Cat-2 is >= -3 & <- 2 LAZ(Moderate Stunting); Cat-3 is >=-2 LAZ(No Stunting)

Figure 3: Mean cognitive z-score at 16 and 24 months at different LAZ levels measured at previous timepoint (9 & 16 months)



Note: Cat-1 is <-3 LAZ(Severe Stunting); Cat-2 is >= -3 & <- 2 LAZ(Moderate Stunting); Cat-3 is >=-2 LAZ(No Stunting)

CHAPTER III: IMPLICATIONS

Summary

Chronic malnutrition among under-five children has been identified as a critical factor preventing these children from reaching developmental potential. This pathway could be linked through improper cognitive development. Considering WHO guidelines and national governmental policies to address chronic malnutrition, the consequences of linear growth failures in terms of cognitive development during early childhood remains unclear. This study considers linear growth as a potential determinant of early motor and cognitive development.

Among our study population, we observed a decrease in mean LAZ scores from -1.1 at 3 mo to -2.3 at 16 mo (Table 2). This decline in LAZ scores suggests worsening of growth with age. This finding aligned with the general trend of stunting in Bangladesh. The prevalence of stunting in Bangladesh increases with age, from 14 percent of children under age 6 months to 46 percent of children 18-23 months (47).

Our analysis showed that LAZ score was significantly associated with both motor and cognitive development during the first 24 mo of life. With each unit increase in LAZ score, there was a significant increase in motor z-scores (Range: 0.10 - 0.16) and cognitive z-scores (Range:0.11- 0.12). However, the association between Length and motor development as well as cognitive development was highest at 16 mo. Along with LAZ scores, BMI z-score was a significant predictor of the motor as well as cognitive z scores. Additionally, maternal education and intervention were also significantly associated with motor and cognitive development.

Public Health Implications

Cognitive development cannot be undermined as it has an inter-generational effect (48). The early years of a child's life provide the best opportunity for physical nourishment and brain development. Stunting signals that the child has been deprived of nutrients for linear growth. Our findings suggest that the motor and cognitive development, could be affected by stunting as early as 3 mo. This evidence supports the need for nutritional interventions during pregnancy, which is likely to have a greater impact on a child's growth (49). However, the intervention should be delivered in the form of a package, including prevention and control of prenatal infections, care of the woman and child and stimulation of early development to address the multicausal problem of stunting. Although exclusive breastfeeding and adequate complementary food, catch-up-growth can be achieved, benefits to cognitive development are uncertain. The CARE intervention involved behavior change communication (BCC) activities and multiple micronutrient supplementation. The study found the intervention to be significantly associated with an increase in the motor and cognitive scores. Thus, instead of focusing on a single approach, a multipronged approach including; nutritional supplement, fortification, deworming pills, and BCC activities should be taken to address stunting and poor child development. Considering the higher prevalence of stunting in Bangladesh, public health intervention at scale focusing on pregnant women and infants should be implemented to avoid consequences of stunting on poor child development.

Possible Future Directions

Although multiple mechanistic pathways linking linear growth retardation and motor or cognitive development have been proposed, the precise mechanism is not well understood. Furthermore, a child's motor, psychosocial, and cognitive development

occurs interactively and dynamically with significant influence from their social environments (47). The lack of focus of the present study on mechanistic assessment prohibits a definitive layout of a framework for pathways and mediators. Thus, taking present evidence further, future studies should be focused on identifying a definitive pathway linking linear growth (retardation) to the motor or cognitive development. Also, the linkage between CARE intervention and LAZ score was not explored. Thus, the association between various components of interventions and LAZ scores could be studied to develop the most effective strategy to prevent and control the problem of stunting as well as child development.

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APPENDICES

1. Supplementary tables

Table 6A: Results of linear models for motor development z-scores

| Parameter | 9 mo | 95% CI | 16 mo | 95% CI | 24 mo | 95% CI |
|----------------------------|-----------|-----------------|-------|------------------|-------|-----------------|
| Intercept | 0.04 | -0.15, 0.22 | 0.21 | 0.01, 0.41 | -0.11 | -0.31, 0.08 |
| LAZ score | 0.11 | 0.07, 0.14 | 0.16 | 0.12, 0.2 | 0.12 | 0.08, 0.16 |
| Intervention | 0.15 | 0.06, 0.24 | -0.03 | -0.12, 0.06 | 0.94 | 0.86, 1.02 |
| Wave | | | | | | |
| Wave 1 | Ref | | Ref | | Ref | |
| Wave 2 | - 0.07 | -0.18, 0.03 | -0.21 | -0.31, - 0.1 | 0.06 | -0.04, 0.16 |
| Wave 3 | 0.14 | 0.03, 0.25 | -0.25 | -0.35, - 0.14 | -0.2 | -0.3, - 0.11 |
| BMIZ score | 0.11 | 0.08, 0.15 | 0.09 | 0.05, 0.13 | 0.07 | 0.03, 0.11 |
| Initiation of CF > 6 mo | 0.14 | 0.026, 0.25 | 0.04 | -0.069, 0.16 | 0.06 | -0.04, 0.17 |
| Maternal Education | | | | | | |
| No Education | Ref | | Ref | | Ref | |
| Primary | 0.10 | -0.004, 0.21 | 0.17 | 0.06, 0.28 | 0.04 | -0.06, 0.15 |
| Secondary | 0.20 | 0.09, 0.32 | 0.38 | 0.26, 0.5 | 0.16 | 0.05, 0.27 |
| Higher | 0.14 | -0.39, 0.68 | 0.31 | -0.21, 0.84 | 0.17 | -0.34, 0.67 |
| Birth order | - 0.03 | -0.08, 0.03 | 0.03 | -0.03, 0.08 | -0.02 | -0.06, 0.03 |
| Exclusive Breastfeeding | - 0.08 | -0.18, 0.03 | 0.02 | -0.09, 0.13 | 0.02 | -0.08, 0.12 |
| Sex | - 0.04 | -0.12, 0.05 | 0.01 | -0.07, 0.1 | -0.12 | -0.2, - 0.04 |

Note: LAZ score: length-for-age z-score; BMIZ score: BMI-for-age z-score; CF: Complementary Feeding

Note: The LAZ scores were lagged at 3, 9 and 16 mo for calculation of coefficient at 9, 16 and 24 mo respectively

Table 6B: Results of linear models for cognitive development z-scores

| Parameter | 9 mo | 95% CI | 16 mo | 95% CI |
|----------------------------|-------|--------------|-------|---------------|
| Intercept | -0.01 | -0.21, 0.19 | -0.22 | -0.44, -0.004 |
| LAZ score | 0.11 | 0.07, 0.15 | 0.10 | 0.05, 0.14 |
| Intervention | 0.11 | 0.02, 0.20 | 0.31 | 0.22, 0.40 |
| Wave | | | | |
| Wave 1 | Ref | | Ref | |
| Wave 2 | 0.03 | -0.07, 0.13 | 0.31 | 0.20, 0.42 |
| Wave 3 | 0.07 | -0.03, 0.18 | 0.19 | 0.07, 0.30 |
| BMIZ score | 0.10 | 0.06, 0.14 | 0.02 | -0.03, 0.06 |
| Initiation of CF > 6 mo | -0.05 | -0.159, 0.07 | 0.11 | -0.004, 0.23 |
| Maternal Education | | | | |
| No Education | Ref | | Ref | |
| Primary | 0.21 | 0.1, 0.32 | 0.08 | -0.04, 0.19 |
| Secondary | 0.40 | 0.28, 0.52 | 0.14 | 0.02, 0.27 |
| Higher | 0.49 | -0.04, 1.01 | 0.13 | -0.45, 0.70 |
| Birth order | -0.03 | -0.08, 0.02 | 0.02 | -0.04, 0.07 |
| Exclusive Breastfeeding | 0.01 | -0.09, 0.12 | -0.04 | -0.15, 0.07 |
| Sex | 0.04 | -0.04, 0.13 | 0.003 | -0.08, 0.09 |

Note: LAZ score: length-for-age z-score; BMIZ score: BMI-for-age z-score; CF: Complementary Feeding

Note: The LAZ scores were lagged at 3, 9 and 16 mo for calculation of coefficient at 9, 16 and 24 mo respectively

2. IRB approval letter- Emory



Institutional Review Board

Date: February 23, 2011

RE: Determination: Not Engaged in Human Subjects Research; IRB Review Not Required [eIRB#00045992]; Monitoring growth and nutritional status of children and their mothers in Bangladesh
PI: Aryeh Stein

Dear Dr. Stein:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because you and Emory will not be "engaged" in research with human subjects. To reach this conclusion we consulted the current guidance on engagement issued by the U.S. Office for Human Research Protections.

Specifically, in this project you will be serving as a consultant assisting in the design and analysis of an evaluation taking place in Bangladesh. All Emory investigators will only be interacting with de identified data. Given the not engaged status of Emory, no Emory investigator should be listed on the consent document and the consent used should be the one from the main study. It was also noted that the local IRB granted an approval period of 24 months; however we would suggest you recommend for them to conduct an annual review.

This determination could be affected by substantive changes in your role or Emory's role in the project. If such changes occur, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Andrea Goosen, MPH
Research Protocol Analyst
This letter has been digitally signed

3. Study Protocol Approval- Bangladesh

**Memorandum**

29 December 2010

To: Dr ASG Faruque
Principal Investigator of research protocol # PR-10093
Clinical Sciences Division (CSD)

From: Professor AKM Nurul Anwar
Chairman
Ethical Review Committee (ERC)

Sub: Approval of research protocol # PR-10093

Thank you for your memo dated 28 December 2010 attaching the modified version of your research protocol # PR-10093 entitled "**Monitoring Growth and Nutritional Status of Children in Rural Bangladesh**" addressing the issues raised by the reviewer to the satisfaction of the Committee. Accordingly, the Committee approved the research protocol. I have pleasure to inform you that your above protocol is approved through expedited review mechanism. You will be required to observe the following terms and conditions in implementing the research protocol:

1. As Principal Investigator, the ultimate responsibility for scientific and ethical conduct including the protection of the rights and welfare of study participants vest upon you. You shall also be responsible for ensuring competence, integrity and ethical conduct of other investigators and staff directly involved in this research protocol.
2. You shall conduct the study in accordance with the ERC-approved protocol and shall fully comply with any subsequent determinations by the ERC.
3. You shall obtain prior approval from the Research Review Committee and the ERC for any modification in the approved research protocol and/or approved consent form(s), except in case of emergency to safeguard/eliminate apparent immediate hazards to study participants. Such changes must immediately be reported to the ERC Chairman.
4. You shall recruit/enroll participants for this study strictly adhering to the criteria mentioned in the research protocol.
5. You shall obtain legally effective informed consent (i.e. consent should be free from coercion or undue influence) from the selected study participants or their legally responsible representative, as approved in the protocol, using the approved consent form prior to their enrollment in this study. Before obtaining consent, all prospective study participants must be adequately informed about the purpose(s) of the study, its methods and

procedures, and also what would be done if they agree and also if they do not agree to participate in the study. They must be informed that their participation in the study is voluntary and that they can withdraw their participation any time without any prejudice. Signed consent forms should be preserved for a period of at least five years following official termination of the study.

6. You shall promptly report the occurrence of any Adverse Event or Serious Adverse Event or unanticipated problems of potential risk to study participants or others to the ERC in writing within 24 hours of such occurrences.
7. Any significant new findings, developing during the course of this study that might affect the risks and benefits and thus influence either participation in the study or continuation of participation should be reported in writing to the participants and the ERC.
8. Data and/or samples should be collected and interviews should be conducted, as specified in the ERC-approved protocol, and confidentiality must be maintained. Data/samples must be protected by reasonable security, safeguarding against risks such as their loss or unauthorized access, destructions, used by others, and modification or disclosure of data. Data/samples should not be disclosed, made available to or use for purposes other than those specified in the protocol, and shall be preserved for a period, as specified under Centre's policies/practices.
9. You shall promptly and fully comply with the decision of the ERC to suspend or withdraw its approval for the research protocol.
10. You shall report progress of research to the ERC for continuing review of the implementation of the research protocol as stipulated in the ERC Guidelines. Relevant excerpt of ERC Guidelines and '*Annual/Completion Report for Research Protocol involving Human Subjects*' are attached for your information and guidance.

I wish you success in running the above-mentioned study.

Copy: Director, CSD
Coordination Manager, RA

- 4. Assessment of Motor and cognitive and motor development at 9, 16 & 24 mo
 - a. Motor development at 9 months:

Mother Study ID

5. Infant Motor Development Milestones⁴

Read: Now I would like to ask you about (INFANT NAME).

| | | | |
|-----|---------------------------|-----------------|---|
| 5.1 | How old is (INFANT NAME)? | | |
| | | Days | <input type="text"/> <input type="text"/> |
| | | Months | <input type="text"/> <input type="text"/> |
| | | 88 = Don't Know | |

Read: Now I would like to specifically begin with a few questions about how (INFANT NAME) is developing, and his/her ability to move.

| | | | |
|-----|---|--|---|
| 5.2 | Can (INFANT NAME) sit without any help, assistance, or support? | 01 = Yes 02 = No 88 = Don't Know | <input type="text"/> <input type="text"/> |
| 5.3 | Can (INFANT NAME) stand with assistance or support? | 01 = Yes 02 = No 77 = Yes, stands without assistance or support 88 = Don't Know | <input type="text"/> <input type="text"/> |
| 5.4 | Can (INFANT NAME) crawl on his/her hands and knees? | 01 = Yes 02 = No 88 = Don't Know | <input type="text"/> <input type="text"/> |
| 5.5 | Can (INFANT NAME) walk with assistance or support? | 01 = Yes 02 = No 77 = Yes, walks without assistance or support 88 = Don't Know | <input type="text"/> <input type="text"/> |
| 5.6 | Can (INFANT NAME) stand alone, with no assistance or support? | 01 = Yes 02 = No 88 = Don't Know | <input type="text"/> <input type="text"/> |
| 5.7 | Can (INFANT NAME) walk alone, with no assistance or support? | 01 = Yes 02 = No 88 = Don't Know | <input type="text"/> <input type="text"/> |

⁴ WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatrica Supplement 2006;450:86-95.

b. Motor and Cognitive development at 16 months through Ages and Stages Questionnaire- Third edition



This is a translation of Ages & Stages Questionnaires®, Third Edition (ASQ-3TM): A Parent Completed Child Monitoring System, by Jane Squires, Ph.D., and Diane Bricker, Ph.D. Originally published in the United States of America by Paul H. Brookes Publishing Co., Inc. Copyright © 2009 by Paul H. Brookes Publishing Co., Inc. Ages & Stages Questionnaires is a registered trademark and ASQ-3 and the ASQ-3 logo are trademarks of Paul H. Brookes Publishing Co., Inc.

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St ID / / / / / / / /

Ages & Stages Questionnaire ®

Child & Family Information

Child's Name: _____ Date of birth / / / / / / / / Sex: M=1, F=2 / /

Mother's name: _____ Age: / / / Father's name: _____

Address: Bari name: _____ Vill: _____

Post: _____ Dist: _____ Mobile no: _____

Name of interviewer: _____ Date of interview / / / / / / / /

16 Month (15 month 0 days through 16 month 30 days) Scoring: 10=Yes, 5=Sometimes, 0=No

| Communication | 'হ্যাঁ' | 'মাঝে মাঝে' | 'না' | Score |
|--|---------|-------------|------|-------|
| ১. ওকি বইয়ের ছবিতে হাত দিয়ে দেখায়, ছবিতে চাপড় দেয় অথবা ছবিটি নিতে চেষ্টা করে? | | | | |
| ২. ওকি "মা, বাবা" ছাড়া আরো চারটি বা তার বেশী শব্দ বলতে পারে? (যদি হ্যাঁ হয় তাহলে নামগুলো জিজ্ঞেস করতে হবে এবং গুনতে হবে যেন ৪টি হয়। মাকে উদাহরণ দেয়া যাবে না।) (Probe- আপনার বাচ্চা কি কি শব্দ বলতে পারে?) | | | | |
| ৩. ও কিছুর চাইলে কি সেটা আঙুল দিয়ে দেখায়? | | | | |
| ৪. ওকে গুর চেনা/ ব্যবহারের কোন জিনিস অন্য ঘর/বাইরে থেকে নিয়ে আসতে বললে ওকি তা নিয়ে আসতে পারে? (জামা, বল, গ্লাস ইত্যাদি যা এই ঘরে নেই।) | | | | |



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| Communication | 'হ্যাঁ' | 'মাকে মাঝে' | 'না' | Score |
|--|---------|-------------|------|-------|
| ৫. আপনি কিছু (২টি শব্দ দিয়ে) বললে ওকি শুনে শুনে সেই কথাটি বলে? (যেমন-বাড়ী যাও, মা যায়, বাবা খেলে) (ওর কথা বুঝতে কিছুটা অসুবিধা হলেও হবে।) (Probe- আপনি ওর সামনে কোন কথা বললে ও কি তা অনুকরণ করে?) বাচ্চার বলা বাক্যের একটি উদাহরণ | | | | |
| ৬. ওকি "মা, বাবা" ছাড়া আরো ৮টি বা তার বেশী শব্দ বলতে পারে? (যদি হ্যাঁ হয় তাহলে নামগুলো জিজ্ঞেস করতে হবে এবং শুনতে হবে যেন ৮টি হয়। মাকে উদাহরণ দেয়া যাবে না।) (Probe- আপনার বাচ্চা কি কি শব্দ বলতে পারে?) | | | | |
| মোট নাথার: | | | | |
| Gross Motor | 'হ্যাঁ' | 'মাকে মাঝে' | 'না' | Score |
| ১. মেঝেতে বসিয়ে রাখলে কোন কিছু না ধরে ওকি নিজে নিজে উঠে দাঁড়িয়ে করবে পা সামনের দিকে ফেলতে পারে? | | | | |
| ২. ওকি কোন আসবাবপত্র অথবা অন্য কোন জিনিসের উপরে একা একা উঠতে পারে? যেমন: খাট, চেয়ার ইত্যাদি। | | | | |
| ৩. ওকি কোন কিছু না ধরে হাঁটু ভাজ করে বসে মেঝে থেকে কোন খেলনা তুলে আবার (নিজে নিজে) দাঁড়িয়ে যায়? | | | | |
| ৪. হামাগুড়ি না দিয়ে ওকি অল্প অল্প হাঁটতে পারে? | | | | |
| ৫. একটু আঁচু পড়ে গেলেও ওকি ভালোভাবে হাঁটতে পারে? | | | | |
| ৬. কোন কিছু করতে বা ধরতে চাইলে ওকি একা একা চেয়ারের উপর উঠতে পারে? (যেমন- কোন খেলনা তাকের উপর থেকে নেয়ার জন্য।) | | | | |
| মোট নাথার: | | | | |
| Fine Motor | 'হ্যাঁ' | 'মাকে মাঝে' | 'না' | Score |
| ১. ওকি আপনার সাহায্যে বইয়ের পাতা উল্টায়? (আপনি একটা পাতা ওর জন্য ধরে রাখতে পারেন।) | | | | |
| ২. ওকি সামনের দিকে ছোট বল ছুঁড়ে মারতে পারে? (যদি বলটি ফেলে দেয় স্কোর পাবে না।) | | | | |
| ৩. ওকি একটি গুটি বা খেলনার উপরে আরেকটি গুটি বা খেলনা রাখতে পারে? (সুতার রীল, ম্যাচবক্স/ছোটবাক্স বা ১ ইঞ্চি মাপের ছোট খেলনা।) | | | | |



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| Fine Motor | 'হ্যাঁ' | 'মাঝে মাঝে' | 'না' | Score |
|--|---------|-------------|------|-------|
| ৪. ওকি নিজে নিজে ৩টি গুটি বা খেলনা একটার উপরে একটা রাখতে পারে? (সুতার রীল, ম্যাচবক্স/ছোটবাক্স বা ১ ইঞ্চি মাপের ছোট খেলনা) | | | | |
| ৫. ওকি আঁকার সময় কলম অথবা পেন্সিলের মাথা/ সামনের দিক দিয়ে কাগজের উপর দাগ দেয়? | | | | |
| ৬. ওকি নিজে নিজে বইয়ের পাতা উল্টাতে পারে? (একবারে কয়েকটি পাতা উল্টালেও হবে।) | | | | |
| মোট নাখার: | | | | |
| Problem Solving | 'হ্যাঁ' | 'মাঝে মাঝে' | 'না' | Score |
| ১. গুর সামনে কাগজের উপর পেন্সিল/রং পেন্সিল দিয়ে কোন কিছু আঁকাআঁকি করলে ও কি আপনার দেখাদেখি আঁকাআঁকি করে? (যদি ও নিজে থেকে আঁকতে পারে 'হ্যাঁ' স্কোর পাবে।) | | | | |
| ২. ও কি একটা স্বচ্ছ বোতলে কোন জিনিসের ছোট টুকরা ফেলতে/ছুকাতে পারে? যেমন- প্লাস্টিকের বোতল বা ফীডার। | | | | |
| ৩. ও কি কতগুলো ছোট খেলনা একটার পর একটা কোন বাটিতে বা বাক্সে ফেলতে পারে? | | | | |
| ৪. অল্প দূরে রাখা কোন জিনিস একটি চামচ বা লাঠি দিয়ে কিভাবে কাছে আনা যায় তা দেখিয়ে দিলে ওকি আপনার মত করে কাছে আনার চেষ্টা করে? | | | | |
| ৫. গুর হাতে একটি পেন্সিল/রং পেন্সিল দিলে ও কি নিজে থেকেই আঁকাআঁকি করে? (ওকে দেখিয়ে না দিলে।) | | | | |
| ৬. বোতলের ভিতর কোন ছোট জিনিস ঢুকালে ও কি বোতল উল্টিয়ে/ উপুড় করে সেটাকে বের করে আনতে পারে? (আপনি চাইলে তা করে দেখাতে পারেন।) | | | | |
| মোট নাখার: | | | | |
| (*** ৫ নাখার Item 'হ্যাঁ' অথবা 'মাঝে মাঝে' স্কোর পেলে ১ নাখার Item 'হ্যাঁ' স্কোর পাবে।) | | | | |
| Personal Social | 'হ্যাঁ' | 'মাঝে মাঝে' | 'না' | Score |
| ১. খাবার পড়ে গেলেও (ফেলে ছেড়ে) ও কি চামচ দিয়ে নিজে নিজে খেতে পারে? | | | | |
| ২. জুতা, মোজা, টুপি খোলার সময় ওকি আপনার সাথে সাথে খুলতে চেষ্টা করে? | | | | |
| ৩. ও কি মানুষ/ প্রানী জাতীয় নরম পুতুল জড়িয়ে ধরে খেলে? | | | | |
| ৪. আয়নায় নিজেকে দেখলে ওকি তার খেলনাটি আয়নায় দেখা নিজের ছবিটাকে দিতে চায়? (খেলনা দিয়ে আয়নায় বাড়ি মারলেও 'হ্যাঁ' স্কোর পাবে) | | | | |
| ৫. আপনি যাতে গুর দিকে খেয়াল করেন অথবা যদি আপনাকে কিছু দেখাতে চায় তখন কি আপনার হাত বা জামা ধরে টানে? | | | | |
| ৬. কোন কাজে সাহায্যের দরকার হলে ওকি আপনার কাছে আসে যেমন- বোতলের মুখ খুলতে অথবা তার খেলনা ঠিক করতে? | | | | |
| মোট নাখার: | | | | |



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OVERALL

১. ওকি কানে ঠিকমত শুনে? হ্যাঁ=১, না=০ /__/
২. ওর সমবয়সী অন্যান্য বাচ্চাদের মত কথা বলতে পারে? হ্যাঁ=১, না=০ /__/
৩. ও যা যা বলে তার বেশিরভাগ কি আপনি বুঝতে পারেন? হ্যাঁ=১, না=০ /__/
৪. সমবয়সী অন্য বাচ্চাদের মত ও কি হাটতে, দৌড়াতে এবং কোনকিছুতে উঠতে পারে? হ্যাঁ=১, না=০ /__/
৫. আপনাদের বংশে কারো কি কানে কম শনার কোন সমস্যা ছিল/আছে? হ্যাঁ=০, না=১ /__/
৬. ও চোখে ঠিকমত দেখে কি না এ ব্যাপারে আপনার কোন সন্দেহ আছে কি? হ্যাঁ=০, না=১ /__/
৭. ওর অন্য কোন ধরনের অসুস্থতা আছে কিনা? হ্যাঁ=০, না=১ /__/
৮. ওর আচরণগত কোন সমস্যা আছে কিনা? হ্যাঁ=০, না=১ /__/
৯. ওর কি অন্য কোন ধরনের সমস্যা আছে? হ্যাঁ=০, না=১ /__/

- c. Motor and cognitive development at 24 months through CDC questionnaire

Mother Study ID

| | | | |
|--|--|--|--|
| | | | |
|--|--|--|--|

12. Child Cognitive Development⁷

Instruction: You (interviewer) will be staying in the household for a long time. Try to observe the child's activity and match those while taking the responses.

Record 01 for "Yes" or 02 for "No" for each question.

Language/Communication

| | | Yes (01) | No (02) |
|------|--|-------------|------------|
| 12.1 | Does your child point to things or pictures when they are named? | | |
| 12.2 | Does your child know names of family members? | | |
| 12.3 | Does your child say sentences with 2 to 4 words | | |
| 12.4 | Does your child follow simple instructions? (You may say, "Bring me your shoes." or "Go, get your blanket.") | | |
| 12.5 | Does your child repeat words overheard in conversations? | | |

Social/Emotional

| | | Yes (01) | No (02) |
|------|--|-------------|------------|
| 12.6 | Does your child copy others, especially adults and older children? | | |
| 12.7 | Does your child gets excited when with other children | | |
| 12.8 | Is your child showing more independence? (Wants to eat meals or put on clothes by him/herself) | | |
| 12.9 | Does your child show defiant behavior? (Does not listen when you tell him/her NOT to do something) | | |

Problem solving

| | | Yes (01) | No (02) |
|-------|--|-------------|------------|
| 12.10 | Can your child find things hidden under two or three covers/sheets? | | |
| 12.11 | Does your child recognize shapes and colors? | | |
| 12.12 | Does your child use one hand more than the other? | | |
| 12.13 | Does your follow simple instruction? (When you ask him/her "Pick up your shoes and put them under the bed.") | | |

Movement/Physical development

| | | Yes (01) | No (02) |
|-------|--|-------------|------------|
| 12.14 | Does your child stand on tiptoe? | | |
| 12.15 | Does your child kick a ball? | | |
| 12.16 | Does your child run? | | |
| 12.17 | Does your child climb onto and down from furniture without help? | | |

⁷ Adapted from CDC's Developmental Milestones for 2-year olds (www.cdc.gov/actearly)

Mother Study ID

| | | | |
|--|--|--|--|
| | | | |
|--|--|--|--|

| | | | |
|-------|--|--|--|
| 12.18 | Does your child make or copies straight lines and circles? | | |
|-------|--|--|--|

Overall

| | | Yes (01) | No (02) |
|-------|---|-------------|------------|
| 12.19 | Do you think your child hears well? | | |
| 12.20 | Do you think your child talks like other toddlers of his age? | | |
| 12.21 | Can you understand most of what your child says? | | |
| 12.22 | Do you think your child walks, runs and climbs like other toddlers of her age? | | |
| 12.23 | Does either parent have a family history of childhood deafness or hearing impairment? | | |
| 12.24 | Do you have concerns about your child's vision? | | |
| 12.25 | Has your child had any medical problem in the last several months? | | |
| 12.26 | Do you have any concerns about your child's behavior? | | |
| 12.27 | Does anything about your child worry you? | | |