The Journal of Nutrition
Community and International Nutrition

See corresponding commentary on page 190.

Daily Supplementation With Egg, Cow Milk, and Multiple Micronutrients Increases Linear Growth of Young Children with Short Stature

Mustafa Mahfuz,[1,2] Mohammed Ashraful Alam,[1] Subhasish Das,[1] Shah Mohammad Fahim,[1] Md Shabab Hossain,[1] William A Petri Jr,[3] Per Ashorn,[2] Ulla Ashorn,[2] and Tahmeed Ahmed[1]

[1]icddr,b, Dhaka, Bangladesh; [2]Faculty of Medicine and Life Sciences, University of Tampere, Finland; and [3]University of Virginia, Charlottesville, VA, USA

ABSTRACT

Background: Childhood stunting is the most prevalent public health nutrition problem in low- and middle-income countries.

Objective: This study aimed to determine whether daily supplementation in 12–18-mo-old undernourished Bangladeshi children with egg, cow milk, and multiple micronutrients improves linear growth.

Methods: In the Bangladesh Environmental Enteric Dysfunction (BEED) study, a community-based intervention study, 12–18-mo-old children with length-for-age *z* score (LAZ) <1 were supplemented daily with an egg and 150 mL of milk for 90 feeding days, and 1 sachet of multiple micronutrient powder was provided daily for 60 feeding days. The change in LAZ over this period was compared with that in children of the same age and same baseline LAZ who were enrolled in the recently completed Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) Dhaka birth cohort study conducted in the same community where no nutrition intervention was provided. Difference-in-difference (DID) analysis was done and the effect size was adjusted for other possible covariates using a generalized estimating equation in a regression model.

Results: A total of 472 children with LAZ <1 completed the intervention and data were available for 174 children in the comparison group. Compared with the comparison group, adjusted DID analysis revealed a change in LAZ in the intervention group of +0.23 (95% CI: 0.18, 0.29; $P < 0.05$). In a subgroup analysis, the changes were +0.27 (95% CI: 0.18, 0.35; $P < 0.05$) in stunted (LAZ <2) children and +0.19 (95% CI: 0.12, 0.27; $P < 0.05$) in children at risk of stunting (LAZ −1 to −2). No allergic reactions or other adverse events related to milk and egg consumption were observed.

Conclusions: Daily directly observed milk, egg, and multiple micronutrient supplementation may improve linear growth of stunted children. A randomized controlled trial with longer duration of supplementation coupled with an additional intervention aimed at reducing pathogen burden is warranted to confirm these results. This trial was registered at clinicaltrials.gov as NCT02812615. *J Nutr* 2020;150:394–403.

Keywords: stunting, MAL-ED, child, egg, milk, multiple micronutrient, supplementation, Bangladesh

Introduction

Stunting [length-for-age *z* score (LAZ) <2 of the WHO growth standard] (1) is currently the most common form of childhood malnutrition worldwide (2). Stunting was found to be associated with negative health and economic outcomes in later life, including shorter adult height, impaired cognitive development, lower attained schooling, and reduced adult income (3). Together with low birth weight, stunting was responsible for 2.1 million deaths and 91.0 million disabilty-adjusted life years in 2008 (4). Globally, 151 million (22%) children aged <5 y are stunted (5), while in Bangladesh, this proportion was 36% in 2014 (6). Despite being a relatively neglected area of research for many years, stunting has become a major public health priority as the World Health Assembly has called for reducing stunting by 40% between 2012 and 2025 (7).

Stunting is believed to be a result of interplay between multiple causal and contextual factors in resource-poor settings, and has been associated with increased susceptibility to infection and impaired neurocognitive development (8). In

Manuscript received July 7, 2019. Initial review completed August 15, 2019. Revision accepted September 19, 2019.
First published online October 26, 2019; doi: https://doi.org/10.1093/jn/nxz253.

affected children, such growth faltering usually manifests as a steady decline in LAZ between the ages of 6 and 24 mo (9, 10). During this period, the child transitions from predominant breastfeeding to complementary foods that are often deficient in key macro-/micronutrients and low in diversity, while diarrheal disease and exposure to enteropathogens is common (5, 11, 12).

A recent analysis including data from 110 countries showed that the average annual relative reduction in the rate of childhood stunting is 1.8% per year (13). This is far behind the rate of 3.9% that is required to meet the global target set by the World Health Assembly to cut the number of children with stunting to 100 million (7). Despite potential contributions to reductions in morbidity and mortality, no single intervention has demonstrated substantial efficacy in normalizing the linear growth velocity and reversing the consequences of stunting. Based on an assessment of multiple approaches to combat stunting, it has been suggested that scaling up of nutrition-specific interventions might correct about 20% of stunting (5). Given that stunting is a consequence of exposure to a complex mix of insults over time, successful treatment is likely to require addressing the problems of consumption of low-quality/diversity diets and recurrent pathogenic and adverse environmental exposures (14).

Micronutrient deficiencies are an important determinant of childhood undernutrition (8). Cereal-based diets of young infants in developing countries lack essential micronutrients such as zinc, vitamin A, and iron (12). In Bangladesh, micronutrient adequacy is poor and a national survey showed that 33% of children aged <5 y were anemic, 20.5% had vitamin A deficiency, and 44.6% had zinc deficiency (15, 16). Dietary supplementation with multiple micronutrient powder was effective in controlling anemia and other micronutrient deficiencies (17). In Bangladesh, the current recommendation as per the National Strategy for Prevention and Control of Anaemia is to provide a 5 component (zinc, iron, folic acid, vitamin A, and vitamin C) multiple micronutrient powder for 2 mo (18).

A recent study revealed that daily provision of a chicken egg can improve linear growth of young children and reduce stunting (19). Egg is a good source of protein, fatty acids, and a range of vitamins and minerals (20). Cow milk is a good source of essential nutrients and its consumption is associated with increased circulating insulin-like growth factor (IGF-1) that promotes linear growth of children (21, 22). Both egg and milk are culturally acceptable and locally available in Bangladesh. Here, we used data from the Bangladesh Environmental Enteric Dysfunction (BEED) study to explore whether daily supplementation with a chicken egg and 150 mL of cow milk and essential micronutrients could improve linear growth of 12–18-mo-old Bangladeshi children who were already stunted, or who were at risk for stunting (23).

Supported by the Bill and Melinda Gates Foundation under its Global Health Program. The project investment ID is OPP1136751.
Author disclosures: The authors report no conflicts of interest.
The funder was not involved with the study design, data collection, or data analysis.
Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
Data described in the manuscript, code book, and analytic code will be made available after completion of the parent study upon request through application and approval.
Address correspondence to MM (e-mail: mustafa@icddrb.org).
Abbreviations used: AI, Adequate Intake; BEED, Bangladesh Environmental Enteric Dysfunction study; DID, difference-in-difference; EED, environmental enteric dysfunction; IGF-1, insulin-like growth factor-1; LAZ, length-for-age *z* score; MAL-ED, Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health.

Methods

Study design

This is a community-based nonrandomized comparative intervention study which is a part of the ongoing BEED study with a historical comparison group from the recently completed Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) study (23, 24).

Description of parent studies.

Intervention group. In the BEED study, children aged 12–18 mo with LAZ <1 were enrolled from the study area through community screening. The first child was enrolled in July 16, 2016 and children enrolled until June 30, 2018 were included in the current analysis. After enrollment, the children were provided with directly observed nutrition intervention for 90 feeding d (23).

The inclusion criteria for enrollment in the BEED study include children of either gender, aged between 12 and 18 mo, LAZ <1, and parent(s) or caregivers willing to sign the consent form and bring the child to the study site every day, 6 d/wk, for 90 d of nutritional therapy. Children with severe acute malnutrition, severe anemia (<8 g/dL), tuberculosis, other chronic diseases or any congenital disorder or deformity, an ongoing episode of diarrhea, a history of persistent diarrhea in the past month, or known allergy/intolerance to eggs or milk were excluded (23).

Comparison group. The MAL-ED Bangladesh study was an observational birth cohort study in which infants were enrolled within 3.5 d of birth and followed longitudinally until age 60 mo without any nutrition intervention (24). Data used in the current analysis were collected between June 11, 2011 and September 15, 2013, covering the period in which included children were aged between 14 mo and 17 mo. During the first 24 mo of the study, the children were followed by twice weekly home visits for dietary and morbidity surveillance. Anthropometry was collected monthly from all participants, while data on sociodemography and food security were collected during enrolment and at 6-mo intervals. The detailed methodology of data collection is described elsewhere (25–27).

The inclusion criteria for enrollment in the MAL-ED study were healthy newborn children of either gender, and parent(s) or caregivers willing to sign the consent form and have a plan to stay in the community for the next 2 y. Exclusion criteria were very low birth weight (<1500 g), extremely ill, severe acute malnutrition, severe anemia (<8 g/dL), tuberculosis, other chronic diseases or any congenital disorder or deformity, nonsingleton infant and mother aged <16 y (24–27).

Study settings.

Description of field site. Both BEED and MAL-ED studies were conducted among the residents of Bauniabadh and adjacent slum areas of Mirpur, Dhaka. The population density of the area is one of the highest in Dhaka city, with more than 38,000 people living in each square kilometer. The sociodemographic details of the field site have already been reported (23, 24).

Participants.

Intervention groups. Children aged 12–18 mo were enrolled from the study area with a LAZ of <1. This child cohort was further divided into 2 groups: stunted children (LAZ < −2) and children at risk of being stunted (LAZ <1 to −2).

TABLE 1 Nutrition and health intervention with delivery method provided to children of intervention group[1]

Intervention	Delivery method
Egg	— 1 boiled egg daily, 6 d/wk
Milk	— UHT processed 150 mL whole milk daily, 6 d/wk
Multiple micronutrient powder	— 1 sachet of multiple micronutrient powder a day administered to the child during each feeding session for 2 mo
	— Each sachet contained 12.5 mg iron, 5 mg zinc, 300 μg vitamin A, 150 μg folic acid, and 50 mg of vitamin C (Monimix)
Nutritional counseling	— Parents/caregivers were given nutritional counseling with particular emphasis on adding vegetable oil to the cooked diet as a source of energy, as well as sources of animal-based products (small fish, chicken, or meat) along with regular intake of vegetables

[1] UHT, ultra-high temperature.

Comparison group. The median age of children in the intervention group at baseline was 14 mo. The MAL-ED study was a longitudinal birth cohort with monthly follow-up data available for all children. We extracted data from MAL-ED children with LAZ <1 at 14 mo and follow-up growth data were collected for the subsequent 4 mo (14–18 mo). The comparison group was matched with the intervention group for age and LAZ. In addition, the following features were comparable between the groups: sex, community information, similar frequency of contact with research staff, anthropometry measurement using the same scales, and follow-up performed by the same research team.

Intervention group.

Enrollment, screening, and consenting. Census, screening, and enrollment of the subjects was conducted in the Mirpur area of Dhaka city through household visits. Based on predefined inclusion criteria, field research assistants enrolled the children whose parent(s) or caregivers were willing to consent and bring their child to the nutrition center every day for 90 feeding d to receive nutritional therapy. Parents of the children who met the eligibility criteria were invited to participate and the study was explained to them in detail by a trained research staff. A written informed consent was signed by the mother or the primary caregiver of the participants before enrollment in the study (23).

Detailed procedure of directly observed nutritional therapy. After enrollment, participants were asked to attend the designated nutrition center (established in the Bauniabadh area, Mirpur) daily for nutritional therapy between 10:00 and 11:30 for 90 feeding d to avoid the issue of food sharing at home. The consumption of milk and egg was directly observed by the field staff. Before serving, each shell-less boiled egg was weighed and 150 mL of milk was measured and the total amounts of food offered, consumed, and left over were measured and recorded at each feeding session. One sachet of multiple micronutrient powder (Monimix, Renata Pharmaceuticals) was mixed with milk by 1 of the research staff during daily feeding for 2 mo. This food was given in addition to the regular diet, and the mothers were instructed to continue usual feeding including breastfeeding. The intervention provided in the study was free of cost. In addition to this feeding intervention, caregivers were provided nutritional counseling during each of the feeding session. Nutritional counseling sessions were conducted using communication materials including posters, pictures, and pamphlets. They discussed how to provide a balanced diet, dietary diversity, minimum meal frequency, importance of animal source protein and iodized salt, water-sanitation-hygiene practice, etc. Details of the nutrition intervention are described in **Table 1** and the composition of the supplemental meal is described in **Table 2**. The nutrition intervention started on July 25, 2016 and this analysis includes all the children in the BEED study who completed nutrition intervention by June 30, 2018 ($n = 472$).

This directly observed nutrition intervention was provided for 90 feeding d, 6 d/wk, except for the weekends. Furthermore, some children were followed for >108 d who missed or were reluctant to take the intervention on scheduled feeding d. However, a child was discontinued from the study and referred for medical evaluation if he/she did not take at least 50% of the food offered for 7 consecutive d (23).

Primary outcome.

The primary outcome of this analysis was the change in LAZ of intervention group compared to children in comparison group, conducted in the same settings in Bangladesh.

TABLE 2 Characteristics of the children at baseline in intervention and comparison groups[1]

Indicators	Intervention ($n = 472$)	Comparison ($n = 174$)	*P* value[2]
Age, mo	14 [13, 16]	14 [14, 14]	0.37
Female	236 (50)	90 (51.72)	0.69
Currently breastfeeding	431 (91.31)	168 (96.55)	0.02
WAMI index	0.58 ± 0.14	0.52 ± 0.12	<0.001
Improved sanitation	297 (62.92)	174 (100)	<0.001
Improved source of drinking water	472 (100)	174 (100)	NA
Maternal education, y	5 [2, 7]	5 [2, 7]	0.44
Length-for-age *z* score at baseline	−2.15 ± 0.80	−2.10 ± 0.75	0.48
Weight-for-age *z* score at baseline	−1.71 ± 0.85	−1.65 ± 0.82	0.06
Weight-for-length *z* score at baseline	−0.90 ± 0.87	−0.76 ± 0.94	0.07
Income, US$/mo	157 [124, 241]	97 [72, 133]	<0.001
Maternal height, cm	149.26 ± 5.21	148.52 ± 5.23	0.11
Stool α1-antitrypsin, mg/g	0.30 [0.12, 0.57]	0.42 [0.24, 0.66]	<0.001
Stool myeloperoxidase, ng/mL	2300 [1340, 4380]	5250 [3030, 10,800]	<0.001
Stool neopterin, nmol/L	2480 [1270, 3790]	1380 [714, 2190]	<0.001

[1] Values are means ± SDs, median [IQR], or frequency (percentage). WAMI index, Water-sanitation-hygiene, Asset status, Maternal education status, and monthly Income index.
[2] Student's *t* test, Pearson chi-square test, and Mann-Whitney *U* test, as appropriate.

Data collection, management, and storage.

Data collection tools for this study included case report forms. All the forms were de-identified by coded numbers to maintain participants' confidentiality and to enable tracking throughout the study.

Anthropometry was performed bi-weekly in the intervention group and monthly in the comparison group. To make the groups comparable, we used anthropometry data of the intervention group collected every 28 d. Because children in the intervention group were followed for a median of 108 d to complete 90 d of feeding, anthropometric measurements at 5 time points were available for this analysis. Anthropometric data were collected by trained personnel, through use of scales with high precision. Weight was measured with a Seca digital weighing scale (model 727, Hamburg, Germany) and length was measured with a Seca infantometer (model 416, Seca, Hamburg, Germany). The same weight and length measurement scales were used for both the intervention and comparison groups (23, 24).

In both groups, socioeconomic and demographic data, maternal information, and maternal anthropometry data were collected at baseline. To measure and compare socioeconomic status between the intervention and control groups, we used the composite Water-sanitation-hygiene, Asset status, Maternal education status, and monthly Income index. This index was used in the MAL-ED study and details have been reported elsewhere (28).

The food intake and compliance data for the nutritional intervention (including data on breastfeeding) were collected daily throughout the intervention period (23). A quantitative 24-h recall approach to estimate nutrient and energy intakes from nonbreast milk complementary foods was carried out before and during intervention in a subset of children ($n = 45$). Dietary assessments by 24-h recall were performed twice: before onset of intervention and during intervention. Experienced research staff who were trained by experienced dieticians conducted the dietary assessments. To assist mothers to provide precise quantification of food intake by their children in the last 24 h, standardized measuring utensils and picture of foods with different portion sizes were used. These interviews were conducted without prior notification to mothers. The methods we used have been published elsewhere (15).

Reported daily morbidity data were available for both the intervention and comparison groups. Diarrhea was defined as passage of ≥3 loose stools in 24 h, and fever was defined as an axillary temperature of >99°F (37.2°C) by a mercury thermometer. In the intervention group, morbidity data were collected during daily feeding sessions, and in the comparison group, the morbidity data were collected through twice-weekly home visits (24). As a measure of environmental enteric dysfunction (EED), stool neopterin (GenWay Biotech), myeloperoxidase (Alpco), and α-1 antitrypsin (Biovendor) were assayed with use of commercial ELISA kits. The laboratory methodologies for the assays have already been published (29, 30). In this paper, we used baseline biomarker results for both the intervention and comparison groups.

Quality control of anthropometric data and refresher training.

Anthropometric measurements were conducted by trained field staff following established standard operating procedures. To maintain the precision of the measurements, 5% of the participants were measured a second time within 24 h of each data collection. The measuring equipment was calibrated daily according to the manufacturers' instructions. To ensure the consistency of an anthropometric measurement from 1 rater to another, refresher training was provided on a regular basis to the field staff and the intra-class correlation coefficient was determined every 3 mo. Such training resulted in significant improvement of raters pertaining to anthropometric measurements with a coefficient >0.9 for each of the scales.

Data analysis

Statistical analyses were performed using STATA (Version 13.1, StataCorp). Statistical significance was defined as $P < 0.05$. The distribution of LAZ was checked for normality with a histogram, QQ plot, and tests for kurtosis and skewness. We compared baseline characteristics between intervention groups and comparison group using Student's *t* tests, Pearson chi-square tests, and Mann-Whitney *U* tests, as appropriate. Both parametric and nonparametric approaches were used for analyses and reported as medians and IQR, or mean and SD (31).

Standard biostatistical modeling techniques were used, including review and stabilization of the variance of the outcome distributions, identification of outliers, and inclusion of confounders in the models. Anthropometry data were collected at 5 time points: at baseline before the beginning of the intervention, at time-1, at time-2, at time-3, and after completion of the intervention. The comparison group data were collected every 30 d and the intervention group data were collected every 28 d. The change in LAZ before and after the interventions was compared within each group and between the groups. The difference-in-difference (DID) analysis technique, a quasi-experimental design that uses data from intervention and control groups to make a counterfactual to estimate the intervention effect, was used to measure the true effect of nutritional intervention on LAZ with the following formula:

$$\text{DID} : [(\text{B} - \text{A}) - (\text{D} - \text{C})] \quad (1)$$

where, A = baseline mean LAZ of intervention group, B = endline mean LAZ of intervention group, C = baseline mean LAZ of comparison group, and D = endline mean LAZ of comparison group.

To assess the true effect of nutritional intervention, we used a regression model with a generalized estimating equation as follows:

$$Y_{it} = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{Group} + \delta\,(\text{Time} \times \text{Group}) + \beta_3 X + \varepsilon \quad (2)$$

where, Y_{it} = outcome variable of interest for individual *i* at time *t*, Time = (1) if endline and (0) if baseline, Group = (1) if intervention group and (0) if comparison group, δ = the effect of nutritional intervention, X = other covariates, and ε = error term.

An additional analysis was done similarly where BEED stunted children were compared with MAL-ED stunted children, and BEED at risk of stunting children were compared with MAL-ED at risk of stunting children.

For dietary assessment, 24-h dietary recall data were converted to nutrients using available food composition tables. Details on these food composition tables have been published elsewhere (15). We have calculated nutrient adequacy ratio, which is the ratio of average daily intake and the RDA (15). We used the age-specific RDA from the recommendation developed by the Institute of Medicine, USA (32, 33). We have reported consumption of energy and nutrients as the percentage of RDA, which is also the percentage of nutrient adequacy ratio. Differences between energy and nutrient intakes before and during intervention were tested with use of a sign test, and differences between energy and nutrient intakes between breastfed and nonbreastfed children were tested with a Mann-Whitney *U* test.

Ethical approval

Ethical approvals was obtained from the Institutional Review Board of icddr,b (protocol no: PR-16,007; Version 1.03; March 1, 2016).

Results

A total of 1287 children with LAZ <1 were screened for BEED, of which 616 children were stunted and 670 children were at risk of stunting. A total of 761 children did not meet the inclusion/exclusion criteria and 525 children were enrolled in the study. Among 761 children who were screened out following exclusion criteria, 74% of parents did not sign the consent, 18% of children had severe anemia (Hb <8 g/dL), 5% of children were suffering from illness, and 3% had developmental delays or congenital anomalies. The parents did not sign the

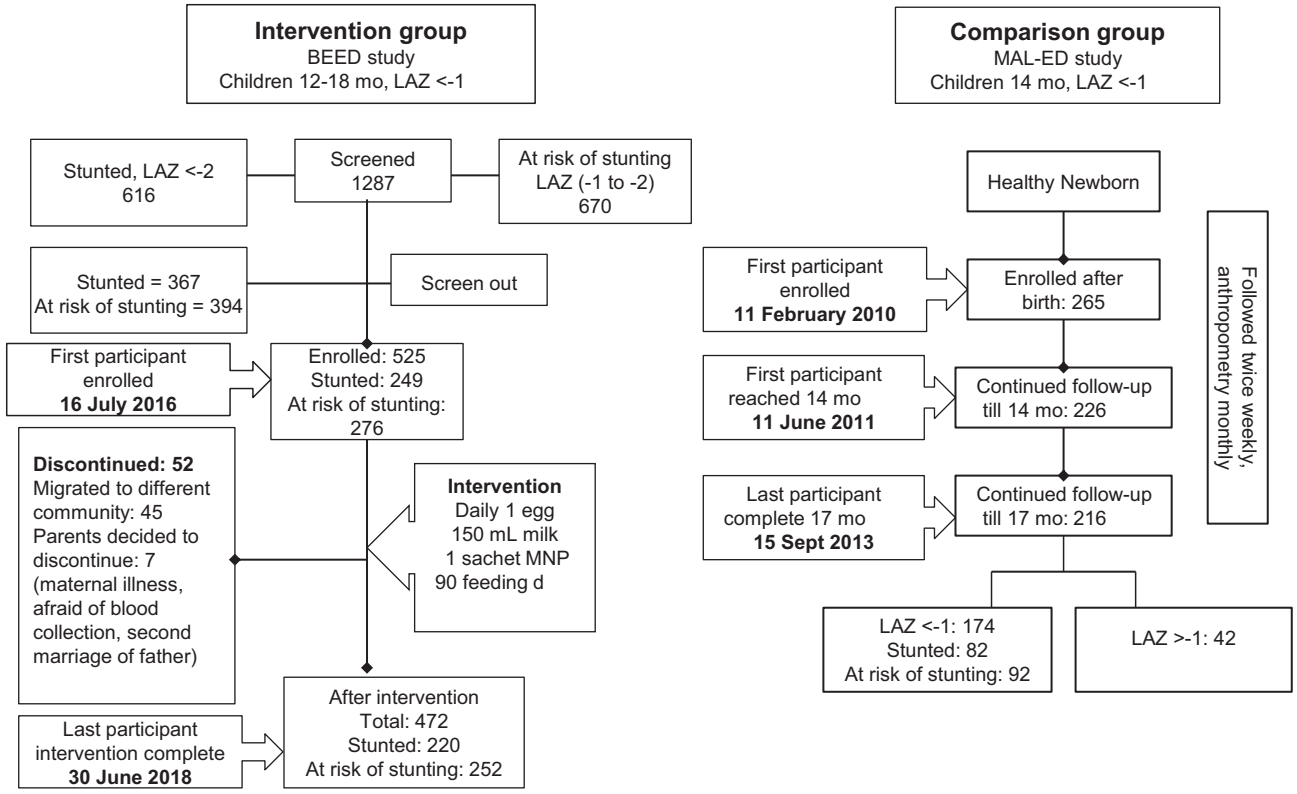

FIGURE 1 Flow diagram of study. BEED, Bangladesh Environmental Enteric Dysfunction study; LAZ, length-for-age *z* score; MAL-ED, Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health; MNP, micronutrient powder.

consent forms for the following reasons: 129 simply refused to enroll their children, 259 refused to provide blood samples, 152 had plans to migrate out from the community, and 3 were working parents. Complete data were available for 472 children (220 stunted children and 252 children at risk of stunting). Fifty-two participants failed to complete the intervention. Of these, 45 migrated out from the community with their family and 7 were withdrawn from the study by their parents for other reasons. The comparison group had complete data for 209 children, collected between the ages of 14 mo to 17 mo of which 174 children had LAZ <1. The enrollment scheme is shown in Figure 1.

At baseline, the median age of children from both groups was 14 mo, and baseline anthropometry including LAZ was comparable between intervention and comparison groups. Stool α-1 antitrypsin and myeloperoxidase concentrations were significantly higher in comparison children compared to intervention, and concentration of neopterin was higher in intervention children than the children from comparison group. Baseline characteristics are described in Table 2.

To achieve directly observed nutrition intervention in the nutrition centers for 90 feeding d, the children were followed for a median (IQR) of 108 (106, 112) d. The average (mean ± SD) number of visits to the nutrition centers made by the stunted children was 89.9 ± 0.18 d, and for the at risk children, it was 86.8 ± 1.2 d. Children were offered daily a boiled egg with a mean (SD) shell-less weight of 56.4 ± 0.9 g and the average egg consumptions of the stunted and at risk of stunting children were 54.7 ± 2.9 g and 54.9 ± 2.9 g, respectively. Compliance of egg consumption was 97% and compliance of milk consumption was 99% for both the groups (Table 3).

Table 4 describes the energy and nutrients provided by each component of the nutritional intervention and the percentage of the RDA provided by the intervention for this age group (32, 33). One egg, 150 mL of milk, and 1 sachet of micronutrient powder provided 33% of the required kcal of energy, 92% RDA of protein, 6% RDA of carbohydrate, 40% RDA of calcium, 188% RDA of iron, and 206% RDA of zinc.

We also collected quantitative dietary intake data of the children before and during nutrition intervention using the 24-h dietary recall approach (Table 5). We observed that before intervention the dietary intakes for energy, protein, carbohydrate, vitamins, minerals, and trace elements were much lower than the age-specific RDAs. On the other hand, dietary intake data collected during nutrition intervention showed a marked improvement of intakes for energy, protein, iron, zinc, vitamins, and other trace elements (Table 5). At baseline, before the start of the intervention, 91% of children were breastfed, and at the end of intervention, still 88% children continued to breastfeed (**Supplemental Table 1**). We also compared nutrient intakes between the breastfed and nonbreastfed children.

TABLE 3 Compliance of daily milk and egg consumption in children of intervention group[1]

Indicators	Values (n = 472)
Egg offered, g	56.4 ± 0.96
Egg consumed, g	54.8 ± 2.95
Egg consumption compliance, %[2]	97.2 ± 4.78
Milk offered, mL	150 ± 0
Milk consumed, mL	148 ± 2.78
Milk consumption compliance, %[2]	98.8 ± 1.86

[1] All values are means ± SDs.
[2] Percentage of egg or milk consumption compliance calculated by [(consumed/offered) × 100].

TABLE 4 Nutritional content and estimated percentage of RDA of each component of nutrition intervention provided to the children of the intervention group[1]

	RDA	Egg (56 g)	Milk (150 g)	MNP (1 g)	Total intake	% of RDA
Energy, kcal/d	548	86.8	92.6	0.00	179	32.7
Protein, g/d	13	7.04	4.97	0.00	12.0	92.4
Fat, g/d	ND	5.94	5.02	0.00	10.9	—
Carbohydrate, g/d	130	0.63	6.98	0.00	7.60	5.85
Calcium, mg/d	500	28.0	175	0.00	203	40.6
Iron, mg/d	7	0.67	0.05	12.5	13.2	189
Zinc, mg/d	3	0.59	0.62	5.00	6.21	207
Copper, mg/d	0.34	0.01	0.02	0.00	0.03	7.50
Vitamin C, mg/d	15	0.00	0.00	30.0	30.0	200
Thiamin, mg/d	0.5	0.04	0.06	0.00	0.10	19.6
Riboflavin, mg/d	0.5	0.29	0.28	0.00	0.57	114
Niacin, mg/d	6	0.04	0.17	0.00	0.20	3.35
Vitamin B-6, mg/d	0.5	0.07	0.05	0.00	0.12	23.6
Folate, μg/d	150	24.6	6.56	160	191	128
Vitamin B-12, μg/d	0.9	0.62	0.54	0.00	1.16	129
Vitamin A, μg/d	300	94.6	43.2	300	438	146
Vitamin E, mg/d	6	0.58	0.09	0.00	0.67	11.2

[1] MNP, micronutrient powder; ND, no available data. RDA is the average daily dietary intake amount, sufficient to meet the nutrient requirements of nearly 97–98% healthy individuals in a group (32, 33).

Energy intake and carbohydrate consumption were significantly higher in nonbreastfed children than the breastfed children. All other estimated nutrients were comparable between the groups (**Supplemental Table 2**).

The mean LAZ of children in the intervention group before, during, and after nutritional intervention in comparison to children in the MAL-ED birth cohort for the same duration are illustrated in **Figure 2**. After adjusting for baseline LAZ, age, sex, mother's height, diarrhea, fever, cough, use of antibiotics, breastfeeding status, and the Water-sanitation-hygiene, Asset status, Maternal education status, and monthly Income index, in a multivariable regression model, DID analysis showed a positive change in LAZ (intervention compared with comparison: coefficient 0.23, 95% CI: 0.17, 0.28, $P < 0.001$) (**Table 6**). After categorizing the children in the intervention and comparison groups into those who were stunted and at risk of stunting, a subgroup DID analysis was performed between stunted children in the 2 groups and the children at risk of stunting in both groups. This analysis yielded similar results (stunted intervention compared with stunted comparison: coefficient 0.27, 95% CI: 0.18, 0.35, $P < 0.001$; at risk of stunting intervention compared with at risk of stunting comparison: coefficient 0.19, 95% CI: 0.12, 0.27, $P < 0.001$) (**Table 7**).

TABLE 5 Nutrient intake of children of intervention group before and during intervention estimated from quantitative 24-h recall data[1]

		Daily intake			% of RDA		
	RDA	Before intervention ($n = 45$)	During intervention ($n = 45$)	P value[2]	Before intervention ($n = 45$)	During intervention ($n = 45$)	P value[2]
Energy, kcal/d	548	396 (43.6, 852)	636 (255, 1120)	<0.001	72.2 (7.9, 155)	116 (46.5, 205)	<0.001
Protein, g/d	13	11.0 (0.6, 32.8)	24.3 (5.7, 46.9)	<0.001	84.8 (4.7, 252)	187 (44.0, 361)	<0.001
Fat, g/d	ND	9.7 (0.2, 36.7)	19.6 (5.7, 39.2)	<0.001	—	—	—
Carbohydrate, g/d	130	56.7 (9.7, 182)	88.1 (36.9, 157)	<0.001	43.6 (7.5, 140)	67.8 (28.4, 121)	<0.001
Calcium, mg/d	500	65.6 (3.7, 645)	258 (23.0, 995)	<0.001	13.1 (0.7, 129)	51.6 (4.61, 199)	<0.001
Iron, mg/d	7	2.2 (0.12, 8.00)	15.3 (13.8, 19.8)	<0.001	31.2 (1.8, 114)	219 (197, 283)	<0.001
Zinc, mg/d	3	1.3 (0.1, 3.89)	7.69 (5.7, 9.5)	<0.001	43.5 (2.7, 130)	256 (189, 316)	<0.001
Copper, mg/d	0.34	0.26 (0.03, 0.6)	0.38 (0.1, 0.8)	<0.001	77.4 (9.7, 201)	112 (32.5, 249)	<0.001
Vitamin C, mg/d	15	6.9 (0.1, 78.2)	40.0 (30.0, 318)	<0.001	46.3 (0.8, 521)	267 (200, 2120)	<0.001
Thiamin, mg/d	0.5	0.17 (0.01, 0.8)	0.34 (0.1, 0.8)	<0.001	34.9 (0.3, 154)	67.7 (27.2, 171)	<0.001
Riboflavin, mg/d	0.5	0.31 (0.002, 1.5)	0.76 (0.1, 1.9)	<0.001	61.5 (0.4, 298)	153 (28.8, 381)	<0.001
Niacin, mg/d	6	3.46 (0.02, 9.8)	4.02 (0.5, 10.7)	0.016	57.6 (0.4, 164)	67.1 (8.04, 178)	0.016
Vitamin B-6, mg/d	0.5	0.4 (0.003, 0.9)	0.53 (0.2, 1.1)	<0.001	74.4 (0.8, 176)	106 (33.9, 212)	<0.001
Folate, μg/d	150	26.2 (0.3, 3)	225 (178, 378)	<0.001	17.5 (0.2, 204)	150 (119, 252)	<0.001
Vitamin B-12, μg/d	0.9	0.5 (0.00, 8.1)	1.49 (0.15, 5.5)	<0.001	59.4 (0.0, 900)	166 (16.1, 608)	<0.001
Vitamin A, μg/d	300	57.8 (0.4, 1820)	486 (307, 1380)	<0.001	19.3 (0.1, 607)	162 (102, 461)	<0.001
Vitamin E, mg/d	6	0.79 (0.005, 3.3)	1.30 (0.4, 7.06)	<0.001	13.2 (0.07, 54.7)	21.7 (7.4, 118)	<0.001

[1] All values are median (min, max). ND, no available data. (An RDA is the average daily dietary intake amount, sufficient to meet the nutrient requirements of nearly 97–98% healthy individuals in a group) (32, 33).
[2] Sign test was performed to test statistical difference.

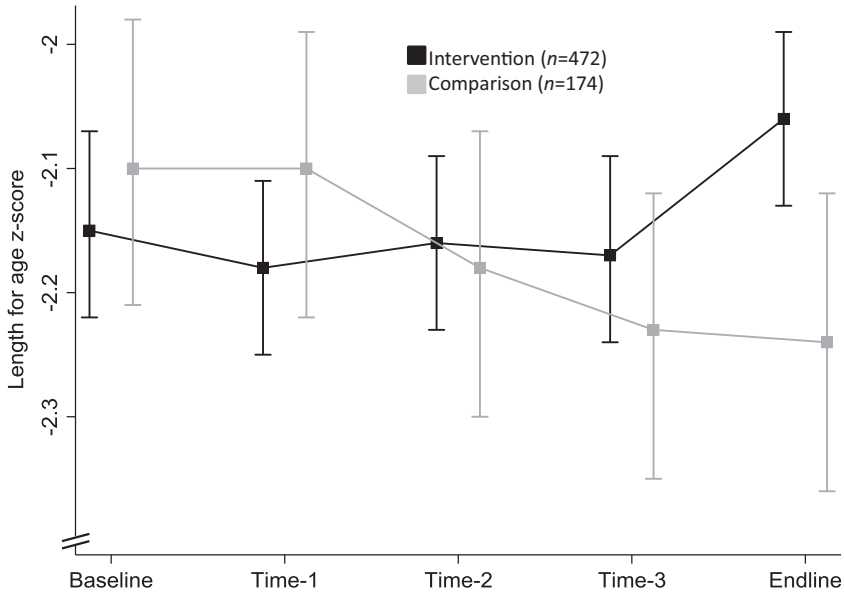

FIGURE 2 Length-for-age *z* score of children in intervention and comparison groups over study period with 95% CI. The comparison group data were collected every 30 d and the intervention group data were collected every 28 d.

We did not observe any allergic reactions or other adverse events related to milk and egg consumption.

Discussion

Our results indicate that stunted and at risk of stunting children who underwent daily dietary supplementation with 150 mL of milk and 1 egg for 90 d and 1 RDA of multiple micronutrient powder for 60 d had better length-for-age *z* scores. We are not aware of any prior study in which stunted children aged 12–18 mo were provided with egg, milk, and multiple micronutrient powder for 90 d to examine changes in LAZ. There are some studies involving intervention with egg, milk, or multiple micronutrient powder alone, although the age group and duration of intervention were not similar to our study (17, 19–22).

In the Lulun project, a randomized controlled trial conducted in Ecuador, 80 infants aged 6–9 mo were provided with 1 egg/d for 6 mo. Egg intervention increased LAZ by 0.63 compared to the control group (19). This is the only published study in which egg was given to young children to improve the linear growth. The effect size for LAZ in the Ecuador trial was substantially higher than any complementary feeding trial conducted earlier (19); the systematic reviews reported earlier showed that the experimental studies with supplementary foods for at least 6 mo among children aged <2 y in food insecure households was associated with a significant improvement in LAZ (standardized mean difference 0.39; 95% CI: 0.05, 0.73) (34, 35). In our study, we observed a positive change in LAZ of 0.24 (95% CI: 0.19, 0.30) in children receiving intervention. It should also be noted that we provided nutrition intervention for only 90 d, every feeding session was directly observed and amounts of egg and milk offered and consumed by children were measured and recorded by research staff.

Egg is a nutritious food and an average 55 g egg contains 75 calories, 7 g protein, 5 g of fat, 1.6 g of saturated fat, vitamins, minerals, and carotenoids (20). Choline, an important precursor of phospholipid, abundant in eggs, is required for cell division and growth (20, 36, 37). In children aged 7–12 mo, an average 50 g egg provides 57% of RDA of protein, 98% Adequate Intake (AI) of choline, and 88% of AI of vitamin B-12, 25–50% of AI for vitamin B-6, folate, phosphorus, and around 20% of AI for zinc (20). In addition to its role in improving linear growth of young children, studies have shown that egg supplementation can improve choline and docosahexaenoic acid status, both are important for growth and neurocognitive development (20). Currently, there are no data on the acceptability of egg in Bangladeshi children. In this study, we observed excellent compliance with egg consumption among children and we did not encounter families that were hesitant to feed their children eggs.

Each 100 g of whole cow milk provides 64 kcal of energy and 3.5 g of protein (21). It also contains important micronutrients and bioactive components that likely contribute to its effects on growth. Studies conducted in developing countries have underscored the considerable benefits of cow milk in stimulating linear growth (21). Observational studies

TABLE 6 DID analysis of LAZ scores between children in intervention and comparison groups[1]

	n	Intervention	*n*	Comparison	DID	*P* value[2]
Baseline	472	−2.15 (−2.22, −2.07)	174	−2.10 (−2.21, −1.98)		
Endline	472	−2.06 (−2.13, −1.99)	174	−2.24 (−2.36, −2.12)	0.23 (0.18, 0.29)	<0.001

[1]All values are mean difference (95% CI) or DID (95% CI). DID, difference-in-difference; LAZ, length-for-age *z* score; WAMI, Water-sanitation-hygiene, Asset status, Maternal education status, and monthly Income index.

[2]Effect of intervention was adjusted for other possible covariates using generalized estimating equation. Adjusted covariates are: age, baseline LAZ, sex, breastfeeding status, mother height, diarrhea, fever, cough, antibiotic use, myeloperoxidase, neopterin, α-1 antitrypsin, and WAMI index. Baseline: before intervention, endline: after completion of intervention.

TABLE 7 Subgroup analyses of stunted and at risk of stunting children in intervention and comparison groups to examine changes in LAZ between the groups[1]

		n	Intervention	*n*	Comparison	DID	*P* value[2]
Stunted children	Baseline	220	−2.82 (−2.90, −2.73)	82	−2.71 (−2.85, −2.58)		
	Endline	220	−2.68 (−2.76, −2.59)	82	−2.84 (−2.98, −2.71)	0.27 (0.18, 0.35)	0.0001
Children at risk of stunting	Baseline	252	−1.56 (−1.59, −1.52)	92	−1.54 (−1.60, −1.49)		
	Endline	252	−1.52 (−1.57, −1.47)	92	−1.70 (−1.79, −1.61)	0.19 (0.12, 0.27)	0.0001

[1] All values are mean difference (95% CI) or DID (95% CI). DID, difference-in-difference; LAZ, length-for-age *z* score; WAMI, Water-sanitation-hygiene, Asset status, Maternal education status, and monthly Income index.
[2] Effect of intervention was adjusted for other possible covariates using generalized estimating equation. Adjusted covariates are: age, baseline LAZ, sex, breastfeeding status, mother's height, diarrhea, fever, cough, antibiotic use, myeloperoxidase, neopterin, α-1 antitrypsin, and WAMI index. Baseline: before intervention, endline: after completion of intervention.

have also demonstrated the growth-stimulating effect of milk in a nutrient-adequate population (21). Growth hormone is less important in early childhood, although its role in child growth starts as early as age 9 mo (38). Growth hormone and nutritional status regulate the synthesis of the insulin-like growth factor-1 (IGF-1) in the liver. In a cohort of stunted Zimbabwean children, amounts of IGF-1 were low and negatively correlated with markers of systemic inflammation (39). IGF-1 increases the uptake of amino acids which are incorporated into new protein including in bone tissue, thereby facilitating bone growth (21). IGF-1 is also involved in calcium and phosphate homeostasis (40), playing an essential role in bone remodeling (41). Hence, by increasing amounts of IGF-1, consumption of cow milk is expected to lead to an increase in linear growth velocity (22, 23).

Micronutrient deficiency, particularly iron, zinc, and vitamin A deficiency, is common in children in developing countries where growth faltering is also high. Zinc deficiency is associated with childhood stunting and supplementation of multiple micronutrient powder can reduce anemia and morbidity, and improve nutritional status (42). In addition to milk and egg, 1 sachet of multiple micronutrient powder containing the RDAs of vitamin A, vitamin C, folic acid, iron, and zinc was provided daily for 2 mo during nutrition intervention. The 24-h recall data indicate that intake of both macro- and micronutrients were improved through the intervention regimen.

Children in the comparison group from the MAL-ED study exhibited gradually worsening LAZ scores between the ages of 15 and 18 mo. The prevalence of stunting in the MAL-ED birth cohort was 18% at 6 mo and increased to 48% at 24 mo (27). In the absence of nutritional supplementation, this is a typical pattern of linear growth faltering in young children living in slum areas of Bangladesh. Nutritional supplementation with milk, eggs, and multiple micronutrient powder improved LAZ scores of children in the intervention group. Despite the comparatively short duration of intervention, this directly observed nutritional supplementation was effective.

Postnatal growth is characterized by an increased linear growth velocity that reduces gradually after birth. The velocity of linear growth of a healthy child is approximately 25 cm per year in the first year and 12 cm from 12 to 24 mo (43). This means that between 12 and 18 mo, a healthy child is expected to grow by 1 cm/mo. We observed that the mean ± SD length increment for stunted and at risk of stunting children were 3.63 ± 0.87 cm and 3.54 ± 0.94 cm, respectively after 90 d of intervention, a higher rate than that of healthy children. On the other hand, during the first year of life, the length velocity is 2.1 cm/mo; this might be the reason why the Lulun trial observed a larger LAZ increase in children who were enrolled at age 6–9 mo.

EED biomarkers between the intervention and comparison groups showed mixed results. α-1 antitrypsin and myeloperoxidase were higher in the comparison group, which means MAL-ED children had more protein loss and intestinal inflammation (30, 44). On the other hand, children in the intervention group had higher concentrations of neopterin. Neopterin is a biomarker of intestinal inflammation and cellular immune activation (30, 44, 45). This also means that over the period of time children in the slums were similarly exposed to pathogens (46, 47).

The egg and milk supplementation provided here was accepted by the children and mothers as judged by the low dropout rates. There were no records of any adverse event, including allergic reactions associated with egg and milk consumption. There are limitations of this study. This was a nonrandomized trial with the absence of concurrent control group. Absence of randomization is prone to major biases and also known to be associated with both overestimation and underestimation of treatment effect (48, 49). The comparison data from the MAL-ED study, collected 3 y before the current study, can be a source of type 1 error and overestimation of treatment effect (50). No nutritional counselling was provided in the control group, thus preventing us from separating the effect of behavior change from the nutritional intervention itself. On the other hand, the duration of supplementation was 90 feeding d, which may be too short to assess the full potential of the intervention on linear growth. Moreover, we did not measure amounts of IGF-1, which may have provided insight regarding potential longer-term efficacy of treatment. Dietary assessment done from a subsample of 45 children might not be representative of all participants under intervention and absence of data on energy and nutrient intakes from breastfeeding is another limitation of this study. Considering cost and complexity of this intervention, and also compared to other research in the same area, the effect size seemed modest. Therefore, justification of this intervention at the programmatic level is subject to further investigation. The role of pathogen burden and its association with childhood stunting observed in the same population (27, 47) were also not addressed. Finally, the inability to identify which of the 3 components of the nutritional intervention was driving the change (or whether all three are required) adds to the cost of the treatment, which may in turn preclude its application in resource-limited programs.

In resource-poor settings with poor maternal education level and high burden of infectious morbidity, directly observed

nutrition therapy with locally available and culturally acceptable nutritious foods (cow milk and egg) with micronutrient supplementation improved linear growth of children aged <2 y. A randomized controlled trial that evaluates the same intervention provided for a longer duration with an additional intervention to reduce pathogen burden with post-intervention follow-up and appropriate control group(s) is warranted to test this hypothesis and further assess the durability of the response to treatment.

Acknowledgments

We acknowledge with gratitude the commitment of the University of Virginia, Washington University in St. Louis, Dhaka Medical College and Hospital, and Bangladesh Specialised Hospital for the research efforts, Environmental Enteric Dysfunction Biopsy (EEDBi) consortium for network-wide coordination, and the MAL-ED network of investigators for use of the MAL-ED Bangladesh data. icddr, b is also grateful to the Governments of Bangladesh, Canada, Sweden, and the UK for providing core/unrestricted support. The authors' responsibilities were as follows—TA and MM: designed the research; TA, MM, SD, and SMF: conducted the research; MM and MAA: performed the statistical analysis; TA, PA, and UA: advised on the analysis; MM and SD: wrote the manuscript; and TA, PA, UA, WP, and SMF: reviewed the draft manuscript; and all authors: read and approved the final manuscript.

References

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–51.
2. Sadler K, Puett C, Mothabbir G, Myatt M. Community case management of severe acute malnutrition in Southern Bangladesh. Medford (USA): Save the Children, Feinstein International Center, 2011.
3. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, Sachdev HS; Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: consequences for adult health and human capital. Lancet 2008;371:340–57.
4. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet 2008;371:243–60.
5. Fanzo J, Hawkes C, Udomkesmalee E, Afshin A, AllemandiL, Assery C, Baker P, Battersby J, Bhutta Z, Chen K, et al. Global Nutrition Report: shining a light to spur action on nutrition. 2018. Bristol (UK): Development Initiatives; 2018.
6. NIPORT/Mitra and Associates/Macro International. Bangladesh Demographic and Health Survey 2011[Internet]. Dhaka: National Institute of Population Research and Training, Mitra and Associates, Macro International; 2012, p. 177[date cited 2019 Mar 14]. Available from: http://dhsprogram.com/pubs/pdf/FR265/FR265.pdf.
7. World Health Organization. Global Targets 2025[last update unknown; cited 2019 Apr 20]. Available from: http://www.who.int/nutrition/topics/nutrition_globaltargets2025/en/.
8. Stewart CP, Iannotti L, Dewey KG, Michaelsen KF, Onyango AW. Contextualising complementary feeding in a broader framework for stunting prevention. Matern Child Nutr 2013;9 (Suppl 2):27–45.
9. Dewey KG, Huffman SL. Maternal, infant, and young child nutrition: combining efforts to maximize impacts on child growth and micronutrient status. Food Nutr Bull 2009;30:S187–9.
10. Victora CG, de Onis M, Hallal PC, Blossner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. Pediatrics 2010;125:e473–80.
11. Prentice AM, Ward KA, Goldberg GR, Jarjou LM, Moore SE, Fulford AJ, Prentice A. Critical windows for nutritional interventions against stunting. Am J Clin Nutr 2013;97:911–8.
12. Dewey KG, Mayers DR. Early child growth: how do nutrition and infection interact? Matern Child Nutr 2011;7(Suppl 3):129–42.
13. de Onis M, Dewey KG, Borghi E, Onyango AW, Blössner M, Daelmans B, Piwoz E, Branca F. The World Health Organization's global target for reducing childhood stunting by 2025: rationale and proposed actions. Matern Child Nutr 2013;9(Suppl 2):6–26.
14. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369:60–70.
15. Sanin KI, Islam MM, Mahfuz M, Ahmed AMS, Mondal D, Haque R, Ahmed T. Micronutrient adequacy is poor, but not associated with stunting between 12–24 months of age: a cohort study findings from a slum area of Bangladesh. PLoS One 2018;13(3): e0195072.
16. National Micronutrients Status Survey 2011–12, Bangladesh. [Internet] Bangladesh: icddr,b UNICEF, Bangladesh, GAIN, Institute of Public Health and Nutrition; 2013[last accessed 2019 Oct 12]. Available from: http://maternalnutritionsouthasia.com/wp-content/uploads/Bangladesh-National-micronutrient-survey-2011-12.pdf.
17. De-Regil LM, Suchdev PS, Vist GE, Walleser S, Peña-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Cochrane Database Syst Rev 2011:(9);CD008959.
18. National Strategy on Prevention and Control of Micronutrient Deficiencies, Bangladesh (2015–2024). Institute of Public Health, Nutrition Directorate General of Health Services, Ministry of Health and Family Welfare, Government of the People's Republic of Bangladesh. 2015.
19. Iannotti LL, Lutter CK, Stewart CP, Gallegos Riofrío CA, Malo C, Reinhart G, Palacios A, Karp C, Chapnick M, Cox K, et al. Eggs in early complementary feeding and child growth: a randomized controlled trial. Pediatrics 2017;140(1):e20163459.
20. Lutter CK, Iannotti LL, Stewart CP. The potential of a simple egg to improve maternal and child nutrition. Matern Child Nutr 2018;14 (Suppl 3):e12678.
21. Hoppe C, Mølgaard C, Michaelsen KF. Cow's milk and linear growth in industrialized and developing countries. Annu Rev Nutr 2006;26: 131–73.
22. Andrea S. Wiley. Chapter 11—Cow's milk consumption and child growth. Dairy in human health and disease across the lifespan. Bloomington (IN): Elsevier Indiana University; 2017, pp. 155–66. DOI:https://doi.org/10.1016/B978-0-12-809868-4.00011-X.
23. Mahfuz M, Das S, Mazumder RN, Masudur Rahman M, Haque R, Bhuiyan MMR, Akhter H, Sarker MSA, Mondal D, Muaz SSA. Bangladesh Environmental Enteric Dysfunction (BEED) study: protocol for a community-based intervention study to validate non-invasive biomarkers of environmental enteric dysfunction. BMJ Open 2017;7(8):e017768.
24. Ahmed T, Mahfuz M, Islam MM, Mondal D, Hossain MI, Ahmed AS, Tofail F, Gaffar SA, Haque R, Guerrant RL, Petri WA. The MAL-ED cohort study in Mirpur, Bangladesh. Clin Infect Dis 2014;59(Suppl 4):S280–6.
25. MAL-ED Network Investigators. The MAL-ED study: a multinational and multidisciplinary approach to understand the relationship between enteric pathogens, malnutrition, gut physiology, physical growth, cognitive development, and immune responses in infants and children up to 2 years of age. Clin Infect Dis 2014;59(Suppl 4): S193–206.
26. Richard SA, Barrett LJ, Guerrant RL, Checkley W, Miller MA, The MAL-ED Network Investigators. Disease surveillance methods used in the 8-site MAL-ED cohort study. Clin Infect Dis 2014;59(Suppl 4):S220–4.
27. MAL-ED Network Investigators. Childhood stunting in relation to the pre- and postnatal environment during the first 2 years of life: the MAL-ED longitudinal birth cohort study. PLoS Med 2017;14(10): e1002408.
28. Psaki SR, Seidman JC, Miller M, Gottlieb M, Bhutta ZA, Ahmed T, Ahmed AS, Bessong P, John SM, Kang G, et al. Measuring socioeconomic status in multicountry studies: results from the eight-country MAL-ED study. Popul Health Metr 2014; 12:8.
29. Kosek M, Guerrant RL, Kang G, Bhutta Z, Yori PP, Gratz J, Gottlieb M, Lang D, Lee G, Haque R, et al. Assessment of environmental enteropathy in the MAL-ED cohort study: theoretical and analytic framework. Clin Infect Dis 2014;59(Suppl 4): S239–47.

30. Fahim SM, Das S, Gazi MA, Mahfuz M, Ahmed T. Association of intestinal pathogens with faecal markers of environmental enteric dysfunction among slum-dwelling children in the first 2 years of life in Bangladesh. Trop Med Int Health 2018;23(11): 1242–50.
31. Fay MP, Proschan MA. Wilcoxon-Mann-Whitney or t-test? On assumptions for hypothesis tests and multiple interpretations of decision rules. Stat Surv 2010;4:1.
32. Trumbo P, Yates AA, Schlicker S, Poos M. Dietary Reference Intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Assoc 2001;101:294–301.
33. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academies Press (US); 1997.
34. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE; Lancet Nutrition Interventions Review Group, the Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 2013;382(9890): 452–77.
35. Lassi ZS, Das JK, Zahid G, Imdad A, Bhutta ZA. Impact of education and provision of complementary feeding on growth and morbidity in children less than 2 years of age in developing countries: a systematic review. BMC Public Health 2013;13 (Suppl 3):S13.
36. Caudill M. Pre- and postnatal health: evidence of increased choline needs. J Am Diet Assoc 2010;110:1198–206.
37. Zeisel SH, Niculescu MD. Perinatal choline influences brain structure and function. Nutr Rev 2006;64:197–203.
38. Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. Acta Paediatr Scand Suppl 1989;350: 70–94.
39. Prendergast AJ, Rukobo S, Chasekwa B, Mutasa K, Ntozini R, Mbuya MN, Jones A, Moulton LH, Stoltzfus RJ, Humphrey JH. Stunting is characterized by chronic inflammation in Zimbabwean infants. PLoS One 2014;9(2):e86928.
40. Kelly O, Cusack S, Cashman KD. The effect of bovine whey protein on ectopic bone formation in young growing rats. Br J Nutr 2003;90: 557–64.
41. Heaney R, McCarron DA, Dawson-Hughes B, Oparil S, Berga SL, Stern JS, Barr SI, Rosen CJ. Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc 1999;99:1228–33.
42. De-Regil LM, Suchdev PS, Vist GE, Walleser S, Peña-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age (Review). Evid Based Child Health 2013;8(1):112–201.
43. Kamboj M. Short stature and growth hormone. Indian J Pediatr 2005;72(2):149–57.
44. Campbell RK, Schulze K, Shaikh S, Mehra S, Ali H, Wu L, Raqib R, Baker S, Labrique A, West KP, Jr, Christian P. Biomarkers of environmental enteric dysfunction among children in rural Bangladesh. J Pediatr Gastroenterol Nutr 2017;65(1):40.
45. Arndt MB, Richardson BA, Ahmed T, Mahfuz M, Haque R, John-Stewart GC, Denno DM, Petri WA, Jr, Kosek M, Walson JL. Fecal markers of environmental enteropathy and subsequent growth in Bangladeshi children. Am J Trop Med Hygiene 2016;95(3): 694–701.
46. Iqbal NT, Syed S, Kabir F, Jamil Z, Akhund T, Qureshi S, Liu J, Ma JZ, Guleria S, Gewirtz A, et al. Pathobiome driven gut inflammation in Pakistani children with environmental enteric dysfunction. PLoS One 2019;14(8):e0221095.
47. Richard SA, McCormick BJ, Murray-Kolb LE, Lee GO, Seidman JC, Mahfuz M, Ahmed T, Guerrant RL, Petri WA, Rogawski ET, Houpt E. Enteric dysfunction and other factors associated with attained size at 5 years: MAL-ED birth cohort study findings. Am J Clin Nutr 2019;110(1):131–8.
48. Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. (Cochrane methodology review). In: The Cochrane Library, issue 4, 2002. Chichester (UK): John Wiley and Sons Ltd, 2002. (http://www.cochrane.org/reviews/clibintro.htm).
49. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7(27):iii–x, 1–173.
50. Viele K, Berry S, Neuenschwander B, Amzal B, Chen F, Enas N, Hobbs B, Ibrahim JG, Kinnersley N, Lindborg S, Micallef S. Use of historical control data for assessing treatment effects in clinical trials. Pharm Stat 2014;13(1):41–54.