A 22-Element Micronutrient Powder Benefits Language but Not Cognition in Bangladeshi Full-Term Low-Birth-Weight Children¹⁻³

Daisy R. Singla,* Sohana Shafique,⁴⁻⁵ Stanley H. Zlotkin,⁴⁻⁶ and Frances E. Aboud

Department of Psychology, McGill University, Montréal, QC, Canada

Abstract

Background: Low-birth-weight children are known to be at risk of both anemia and cognitive/language deficits in their early years.

Objective: The aim of the current study was to examine the effects of a 22-element multiple micronutrient powder (MNP) on the cognitive and language development of full-term low-birth-weight (LBW-T) children in Bangladesh.

Methods: The current study was a follow-up of children who were enrolled in a randomized cluster trial at 7–12 mo of age. Children in 12 intervention clusters (communities) were administered a daily 22-element MNP sachet with their food for 5 mo, and both intervention and control groups (also 12 clusters) received nutrition, health, and hygiene education. The current study involved the assessment of children at 16–22 mo of age (22-element MNP group: n = 96; control group: n = 82) on 3 subtests of the Bayley Scales of Infant and Toddler Development III test to measure cognitive, receptive language, and expressive language development.

Results: There was a significant effect of the 22-element MNP on children’s expressive language scores (d = 0.39), and stunting moderated the effect on receptive language scores; there was no effect on cognitive development (d = 0.08).

Conclusion: An MNP may thus offer one feasible solution to improve language development of LBW-T children in low-resource community settings. This trial was registered at clinicaltrials.gov as NCT01455636. J. Nutr. 144: 1803–1810, 2014.

Introduction

Important questions are being asked about the extent to which malnutrition influences the mental development of children in low- and middle-income countries (LMIC)⁷ (1). Cross-sectional and prospective analyses have shown that iron and iodine deficiencies, in particular, are associated with poor cognitive and language outcomes (2,3). Interventions providing zinc, iron, and FAs have not yielded consistent findings (4–6). Many children are deficient in multiple micronutrients (MMNs), so nutritionists are now examining the effects of MMNs on growth and development (7,8). Low-birth-weight infants are of particular interest, given their high prevalence in LMIC and their predisposed vulnerability to poor iron status, growth, and development outcomes (9). In addition, the first 2 y of life are known to be the most vulnerable, with malnutrition showing long-term effects on health, growth, and development (10,11). Thus, the aim of the current study was to examine the effects of a 22-element multiple micronutrient powder (MNP) on the cognitive and language development of full-term low-birth-weight (LBW-T) children in Bangladesh.

Two recent reviews have summarized the effects of MMNs on mental development (7,8). Together, they included 6 studies on children <5 y of age, although only one measured mental development (10). The remainder for this age group measured gross motor development, particularly walking without support. Although motor development is related to mental development, these 2 domains are different and the connections are weak (12). There is now greater interest in assessing mental development outcomes of nutrition interventions. Our own search resulted in 6 additional studies that provided ≥3 micronutrients for 6 mo to children <2 y
of age; none yielded main effects on mental development (10,13–18). Some studies have shown positive effects on mental development in some groups but not others. For example, Pollitt et al. (17) found beneficial effects from MMNs when combined with energy and given for 12 mo for stunted children but not for taller children. There were no benefits to children given MMNs without energy and no benefits to children who started supplements at 12 mo of age. In summary, more research is needed using various combinations of MMNs in particular with children who vary in their risk of malnutrition.

Low-birth-weight (LBW) children are known to be at risk of cognitive and language deficits particularly in the early years (19,20). The first 2 y are known to be a critical period with long-term consequences for academic school performance (1,21). Recent statistics indicate that the prevalence of LBW is highest in South Asia, where 28% of children are born <2500 g. In Bangladesh, this estimate is even higher at 36% (22). Multiple micronutrients have been used to target LBW children. In India, small-for-gestational-age infants (birth weight <10th percentile weight-for-gestational-age) were administered either a 5- or 6-micronutrient mix (14). Results showed that the addition of zinc conferred no benefits on mental development beyond the 5-element mix. In sum, there is little knowledge about the effects of early cognitive and language development, particularly in vulnerable populations such as LBW-T infants in LMIC.

The weak effects of micronutrient interventions might be due to the inadequate number of nutrients provided, especially for children who are LBW or reside in food-insecure areas. Three mechanisms may account for the effects of micronutrients on development: linear growth, exploration, and brain function. Micronutrients are expected to improve linear growth (23), one of the main correlates of mental development. Linear growth was not significantly improved in the mental development studies cited previously (13–18) but may improve with more micronutrients. In addition, multiple micronutrients led to higher activity and exploration among Mexican infants 8–12 mo of age (24) and may potentially influence brain development in infancy (25).

The primary objective of the 22-element nutrition intervention studied here was to improve linear growth and reduce anemia. The larger trial for which the current study is a follow-up offered a promising context in which to examine the effects of such an intervention on mental development. Consequently, we examined the cognitive and language development of LBW-T children born in rural Bangladesh who were administered a 22-element MNP between 7 and 12 mo of age. This age is important because there is strong potential for physical and mental growth (25). We also examined the role of possible moderators including mother’s education, length for age, and home stimulation because of their relevance in other studies (17).

**FIGURE 1** Flow chart outlining the recruitment and random assignment of participants involved in the larger trial and current study. Control group (nutrition, health, and hygiene education only). Intervention group (22-element MNP plus nutrition, health, and hygiene education). MNP, multiple micronutrient powder.
Materials and Methods

Study design
The current study is a follow-up of children who participated from birth in a larger cluster, randomized, controlled trial with 4 cells (Fig. 1) and 2 phases: phase 1 (children aged 0–6 mo) and phase 2 (children aged 7–12 mo). To examine the effects of MMNs on linear growth and mental development, the current study included children from only 2 cells (n = 186) of the larger study: the MNP intervention (22-element MNP plus nutrition, health, and hygiene education) and the control (nutrition, health, and hygiene education only). In total, the current study included 24 clusters: 12 communities served as intervention clusters and 12 communities constituted the control clusters. The data analyzed here were collected during a follow-up of mothers and their LBW-T children, now 16–22 mo of age. Children outside this age range during the 2.5 mo of testing were excluded. Ethical approval was received from the University of Toronto and the Bangladesh Medical Research Council.

Random assignment and recruitment
Target communities in 2 subdistricts of rural Bangladesh were identified and randomly assigned to intervention or control clusters. Recruitment for the larger trial took place over the course of 6 mo to meet the required sample size. Recruitment stopped once the targeted number of LBW-T newborns was reached. Over this 6-mo period, and prior to data collection for the larger trial, households were visited and mothers who reported being pregnant for ≤4 mo were identified (n = 2918). Research assistants visited the home within 24 h of birth, obtained verbal consent, and weighed the newborn on a Seca scale. At this time, 1293 newborns were weighed and other information relevant to exclusion criteria was collected. Newborns outside the 1800–2499 g range were excluded, along with children who were born at ≥37 wk of gestation and those who experienced asphyxia at delivery. Gestational age was based on the mothers’ report of the date of her last menstrual period (26), taken during the first recruitment visit. To reduce memory bias, only mothers whose period was reported to have occurred within the past 4 mo were retained. All children were born at home. Research assistants who collected this information recruited all eligible newborns, and 14 newborns refused to participate. Children recruited for the current study came from the 24 cluster communities that had been randomly assigned to the control group for phase 1 (when participants were 0–6 mo of age) and so had received educational messages only during the first phase. For phase 2, 12 clusters were randomly assigned to be administered an MNP (n = 117) and 12 only educational messages (n = 114). Of the 321 children in these 24 clusters, 45 (19%) were excluded from the current study because they did not meet age criteria. Random assignment was largely successful and there were no significant differences between the participants in the 4 arms of the larger trial at baseline on various sociodemographic variables.

Participants and sample-size estimation
Participants resided in Palash and Kaliganj, 2 subdistricts located 50–62 km north of the capital city Dhaka. These are rural areas with mainly farmers and wage laborers. A sample-size estimation indicated that 84 children would be required for each group, using an effect size of 0.50 and an α of 0.80. This implied that, on a Bayley Scales of Infant and Toddler Development III test (Bayley III) development scale (27) with a mean of 100 and an SD of 15, the groups would differ by 7.5 points (half of 1 SD). The sample size was multiplied by 1.2 to accommodate clustering, requiring 100 per group.

Intervention and education
Participants from only 2 of the original 4 trial cells were included here, namely an MNP plus nutrition, health, and hygiene education (intervention) and nutrition, health, and hygiene education only (control). Education, received by both groups, comprised key messages related to exclusive breastfeeding, age-appropriate complementary foods, and responsive feeding along with conversation (nutrition); early recognition and home-based care of infections (health); and hand washing with soap (hygiene). Selected individuals from each community called health and nutrition assistants (HNAs) delivered the nutrition, health, and hygiene education. HNAs were aware of the intervention status of the community. However, to ensure the consistency of delivery, HNAs were trained by using a standardized protocol with flipcharts; they also received weekly supervision. Supervisors reported problems related to delivery to 2 field officers; no differences in delivery problems were reported between intervention and control sites. Families from both intervention and control groups received ~35 educational contacts, starting 1 mo before the expected birth at which point mothers were given a safe delivery kit and informed about immediate breastfeeding and hand washing. Both intervention and education components of the study were conducted in the mothers’ homes.

The children in the intervention group also were administered a 22-element MNP daily with their food, between 7 and 12 mo of age (see Supplemental Table 1 for a detailed composition, 28). The sachets were delivered weekly by HNAs to participants’ homes and the full or empty sachets were picked up the following week to determine adherence (above 80% in all clusters). Specifically, adherence was assessed by collecting and counting the total number of MNP sachets used by families each month, as well as with a structured questionnaire in which families were asked whether any child other than the target child was administered the sachets. This was followed-up during a focus group discussion with families to discuss barriers related to intervention delivery. Results from the focus group discussions showed that families reported not sharing the MNP sachets with other children.

Data collection and measurements
Data collection for this study took place on only 1 occasion. Because of a 6-mo rolling enrollment, the follow-up subsample of children assessed for the current study had completed the larger trial 4–10 mo prior to testing. Two research assistants, with master’s degrees in the social sciences, were trained to administer the measures with high interrater reliability (0.85–0.97). One research assistant interviewed mothers and the second administered the Bayley III test to children at their homes. Data were collected between July and September 2012. The research assistants remained unaware of group assignment throughout data collection.

Primary outcome variables included cognitive and language scores on the Bayley III (27). The Bayley III is the best conventionally and internationally used measure of cognitive and language development for children of this age. Three subs tests (cognitive, receptive language, and expressive language) were modified and translated for this population and found to be valid with respect to age and other predictors (29). A number of variables potentially related to mental development were assessed, including the child’s recent illnesses and length for age, parenting practices of the mother, and family sociodemographics. Recent sickness was assessed by asking mothers whether their child was sick in the past week, and if so, whether the child had diarrhea, fever, or respiratory problems. Because recent illness was not associated with other variables, only its prevalence and correlations are reported. Length for age was measured by taking the mean of 2 readings of the child’s length/height by using a locally constructed wooden stadiometer and calculating Z-scores according to international standards for age and gender (30). Weight was measured with a Seca scale and similarly converted into weight-for-age Z-scores.

Parenting practices. Preventive health practices taken from health surveys used in Bangladesh included access to safe water; use of latrines for disposal of child feces; immunization for tuberculosis, diphtheria, tetanus and pertussis, and polio and measles; and whether the child was administered vitamin A drops. The maximum score was 7. To measure dietary diversity, mothers were asked what foods their child ate the previous day. All foods eaten by the child since the family awoke, including cookies, were to be recalled. Quantities were not recorded. Foods were categorized as grains, legumes, animal flesh, eggs, milk, vegetables, and fruits. The dietary diversity score constituted the sum of food categories out of 7 (31). Caregiver provision of psychosocial stimulation was measured by using the Home Observation for the Measurement of the Environment (HOME) Inventory. The HOME Inventory measures opportunities for stimulation of the child in the home by using a 45-item structured observation and interview that is
conducted with the mother and her child at home (32). For example, the interviewer asks the mother to show her the items her child plays with on a usual day, and observes the mother’s responsiveness to her child during the interview. This measure was previously used in Bangladesh and validated against an observational measure of mother-child interaction (13).

 Mothers’ knowledge of child development milestones was assessed with a 6-item measure asking mothers at what age children, in general, acquire specific social and cognitive skills (e.g., when do children recognize their mother, begin to understand words spoken to them, and enjoy seeing color and movement) (29). Generating a total score for this scale (internal consistency α = 0.77), in which higher scores reflect higher knowledge, required the calculation of a reverse score. This is because mothers consistently overestimate the age, which is more inaccurate than lower estimates. To calculate a mother’s score, her mean estimate of the 6 milestones was subtracted from 16 because children normally develop during the first 16 mo of life. Thus, the maximum score for this variable is 16. For example, a mother who estimated that development occurred, on average, at 12 mo would receive a score of 4, whereas one who estimated 18 mo would receive a score of −2.

Sociodemographic variables. Children’s dates of birth were recorded. Mothers were also asked their and their spouse’s age, years of schooling, occupation, and household size. Family assets were measured according to their possession of 11 household items (e.g., bed, chair, latrine, bicycle, television), similar to the Bangladesh Health and Demographic Survey (33). Mothers’ autonomy was also assessed, specifically with regards to mothers’ mobility and decision-making. Two scales have been used previously in Bangladesh (29) and are based on Demographic and Health Survey items. Decision-making questions asked who decides what food to feed and medical care to give the child (5 items) with the following response options: solely the mother (1 point), jointly with someone else (1 point), and no say (0 points). Maternal mobility concerned the freedom to move around the community to access resources such as markets, shops, clinics, and relatives. Response options were the following: alone or with child (2 points), jointly with another same-aged person (1 point), or only with a husband or elder (0 points). Cronbach’s α demonstrated high internal consistency for both decision-making autonomy (α = 0.91) and mobility (α = 0.96).

Method of analysis
The data were analyzed by using the SAS 9.3 statistical package. First, differences between intervention and control groups on all variables except Bayley developmental outcomes were examined by using PROC MIXED ANOVA, which accommodates for clusters. Second, correlates of the 3 Bayley developmental outcomes were calculated by using Pearson’s correlation (r). Findings from these 2 analyses helped to identify covariates for the main analysis of outcomes. The main analysis examined differences between intervention and control groups by using PROC MIXED adjusting for clustering and covariates. Cohen’s d effect sizes were calculated by using the adjusted means and pooled SD. Finally, 3 moderator variables were examined: maternal education, length for age, and HOME scores. Interaction terms were created by first centering each child’s score for that variable around the mean and then multiplying that variable by the intervention variable. Multiple regression analyses were then conducted to determine whether each interaction term independently accounted for a significant amount of the variance for Bayley outcomes, after also entering main effects and covariates. If it did, then post hoc simple main effects analyses were conducted to identify the source of the interaction, by using covariates and the error term from the larger analysis.

Results
A total of 186 LBW children (intervention group: n = 99; control group: n = 87), between 16.0 and 21.8 mo of age, participated in this study. Eight children refused to participate in Bayley testing (3 from the intervention group and 5 from the control group). The scores of all sociodemographic, parenting practices, and child variables are shown in Table 1. Random assignment was largely successful. Differences between the intervention and control groups included mothers’ education (P < 0.04); HOME (psychosocial stimulation) scores were somewhat higher in the intervention group (P < 0.07).

As expected, raw Bayley scores on the 3 subtests correlated significantly with the child’s age (r = 0.19–0.42; P < 0.01). Other child variables such as length for age and weight for age correlated significantly with both cognitive (r = 0.15) and receptive language (r = 0.17–0.21) but not expressive language. Of all the sociodemographic and parenting practice variables, parents’ education, family assets, and HOME scores significantly correlated with all 3 Bayley developmental outcomes (Table 2). Consequently, the analysis of raw Bayley outcomes included the following 5 covariates: child’s age, length-for-age Z-score, mother’s education, family assets, and HOME scores. Child’s age was thus added as a covariate to all statistical analyses with the exception of the age correlations.

Expressive language scores were significantly higher among children in the intervention group than those in the control group (P < 0.02; d = 0.39; Table 3). There were no differences between groups on cognitive or receptive language scores. Child’s gender did not interact with the intervention groups; however, girls overall scored higher on the receptive language test (P = 0.01). This gender difference was not found among cognitive and expressive language scores.

Moderation analyses were conducted to determine whether specific variables influenced the effect of the 22-element MNP on Bayley III developmental outcomes. Specifically, we examined the moderating effects of maternal education, HOME scores, and length for age. Of these 9 analyses (3 moderators × 3 Bayley scores), length for age moderated the effect of the 22-element MNP on receptive language scores (β = 0.94; P < 0.06). To examine the nature of this effect, receptive language scores were compared for children above and below the mean length for age (Z = −2.00) in the control and intervention groups. Among children in the control group, stunted children scored better than stunted children, whereas among those in the intervention group, stunted and nonstunted children did not differ in receptive language scores (Fig. 2).

Discussion
Our main finding was a significant effect from the 22-element MNP on children’s expressive language scores. Stunting moderated the effect of the 22-element MNP on children’s receptive language scores in the control group only, and there was no effect on cognitive development.

Consistent with previous studies (10,13–16), there was no direct effect from the MNP on cognitive development in children of this age. Unlike other studies, however, we did find a significant difference in language development scores between children in the intervention group and those in the control group and more significantly for expressive than receptive language. Three factors may account for the difference between our findings and those of previous studies: 1) our method of assessing language development, 2) a focus on LBW-T children, and 3) the choice of nutritional supplements for the intervention group.

Previous studies have typically used the Bayley Scales of Infant Development II (34) that combines various aspects of mental development into 1 index. In contrast, our study used the more recent Bayley III (27), which assesses specific domains of cognition, receptive language, and expressive language on

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separate subscales. Two published studies did examine language development by using the Griffith Scales in children <24 mo; however, one showed no beneficial effects from an MNP (16) and the other examined the role of gangliosides but not micronutrients (35). It can be expected that future research will use specific language subscales from the newer version of the Bayley. Thus, we may be able to determine if nutrition supplements such as micronutrients affect language more than cognition and whether these differences are more clearly observed in year 2 of life when language is rapidly developing.

LBW children have also been of particular interest because of their known vulnerability during growth and development (1). Previous studies of LBW-T children have reported delays in mental development in the early years, but not thereafter (19,20). Yet, single and multiple micronutrient interventions in these early years have not consistently been effective in supporting mental development of LBW or other high-risk children. For

**TABLE 1** Characteristics of children (16–22 mo of age) and parents in control (nutrition, health, and hygiene education only) and intervention (22-element MNP plus nutrition, health, and hygiene education) groups (n = 186) \(^1\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Range</th>
<th>Control group (n = 87)</th>
<th>Intervention group (n = 99)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child age, mo</td>
<td>16.0–21.8</td>
<td>18.39 ± 1.52</td>
<td>18.27 ± 1.41</td>
<td>0.72</td>
</tr>
<tr>
<td>Girls, %</td>
<td>—</td>
<td>52.3</td>
<td>58.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Recent illness, %</td>
<td>—</td>
<td>26.4</td>
<td>22.2</td>
<td>0.50</td>
</tr>
<tr>
<td>Length-for-age Z-score</td>
<td>−4.04–1.81</td>
<td>−2.06 ± 0.87</td>
<td>−1.96 ± 0.95</td>
<td>0.39</td>
</tr>
<tr>
<td>Weight-for-age Z-score</td>
<td>−4.19–1.36</td>
<td>−1.71 ± 0.88</td>
<td>−1.54 ± 0.88</td>
<td>0.29</td>
</tr>
<tr>
<td>Weight-for-length Z-score</td>
<td>−3.42–2.96</td>
<td>−0.97 ± 0.87</td>
<td>−0.83 ± 1.16</td>
<td>0.59</td>
</tr>
<tr>
<td>Mother’s education, y</td>
<td>0–14</td>
<td>6.09 ± 3.58</td>
<td>7.10 ± 3.44</td>
<td>0.04</td>
</tr>
<tr>
<td>Mother’s age, y</td>
<td>17–42</td>
<td>24.06 ± 4.64</td>
<td>25.04 ± 5.54</td>
<td>0.27</td>
</tr>
<tr>
<td>Father’s education, y</td>
<td>0–15</td>
<td>5.45 ± 4.36</td>
<td>6.01 ± 4.52</td>
<td>0.48</td>
</tr>
<tr>
<td>Household size, no. of residents</td>
<td>3–9</td>
<td>4.9 ± 1.85</td>
<td>5.23 ± 1.85</td>
<td>0.23</td>
</tr>
<tr>
<td>Birth order</td>
<td>1–5</td>
<td>1.88 ± 0.99</td>
<td>2.01 ± 1.15</td>
<td>0.36</td>
</tr>
<tr>
<td>Assets score (out of 11)</td>
<td>2–11</td>
<td>6.75 ± 2.29</td>
<td>6.98 ± 2.24</td>
<td>0.78</td>
</tr>
<tr>
<td>Decision-making score (out of 2)</td>
<td>0–2</td>
<td>1.23 ± 0.48</td>
<td>1.17 ± 0.56</td>
<td>0.41</td>
</tr>
<tr>
<td>Mobility score (out of 2)</td>
<td>0–2</td>
<td>0.53 ± 0.64</td>
<td>0.53 ± 0.63</td>
<td>0.99</td>
</tr>
<tr>
<td>Dietary diversity score (out of 7)</td>
<td>0–6</td>
<td>3.89 ± 1.24</td>
<td>3.89 ± 1.32</td>
<td>0.97</td>
</tr>
<tr>
<td>Preventive score (out of 7)</td>
<td>1–7</td>
<td>5.92 ± 0.94</td>
<td>6.18 ± 0.61</td>
<td>0.10</td>
</tr>
<tr>
<td>HOME Inventory score (out of 45)</td>
<td>18–41</td>
<td>31.40 ± 3.80</td>
<td>32.34 ± 3.31</td>
<td>0.07</td>
</tr>
<tr>
<td>Mother’s knowledge score (^2) (out of 16)</td>
<td>0–13.5</td>
<td>8.86 ± 3.08</td>
<td>8.81 ± 2.85</td>
<td>0.84</td>
</tr>
</tbody>
</table>

\(^1\) Values are means ± SDs unless otherwise indicated. HOME, Home Observation for the Measurement of the Environment; MNP, multiple micronutrient powder.

\(^2\) Values are based on a calculation of mothers’ estimates of children’s milestones in months.

**TABLE 2** Correlates of Bayley III cognitive and language outcomes of the full sample (n = 178) \(^1\)

<table>
<thead>
<tr>
<th>Developmental outcomes</th>
<th>Cognitive (^2)</th>
<th>Receptive language (^3)</th>
<th>Expressive language (^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length-for-age Z-score</td>
<td>0.17*</td>
<td>0.18*</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight-for-age Z-score</td>
<td>0.14</td>
<td>0.22**</td>
<td>0.13</td>
</tr>
<tr>
<td>Weight-for-length Z-score</td>
<td>0.09</td>
<td>0.18*</td>
<td>0.13</td>
</tr>
<tr>
<td>Sickness in the past week</td>
<td>−0.08</td>
<td>−0.04</td>
<td>−0.08</td>
</tr>
<tr>
<td>Mother’s age (y)</td>
<td>0.04</td>
<td>0.04</td>
<td>−0.02</td>
</tr>
<tr>
<td>Mother’s education (y)</td>
<td>0.24**</td>
<td>0.22**</td>
<td>0.18*</td>
</tr>
<tr>
<td>Father’s education (y)</td>
<td>0.13</td>
<td>0.23**</td>
<td>0.12</td>
</tr>
<tr>
<td>Assets score (out of 11)</td>
<td>0.32***</td>
<td>0.28***</td>
<td>0.22**</td>
</tr>
<tr>
<td>Household size (n)</td>
<td>0.12</td>
<td>0.10</td>
<td>0.18*</td>
</tr>
<tr>
<td>Decision-making score (out of 2)</td>
<td>−0.00</td>
<td>−0.16*</td>
<td>−0.18**</td>
</tr>
<tr>
<td>Mobility score (out of 2)</td>
<td>−0.02</td>
<td>−0.12</td>
<td>−0.12</td>
</tr>
<tr>
<td>Preventive score (out of 7)</td>
<td>0.15*</td>
<td>0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Dietary diversity score (out of 7)</td>
<td>0.05</td>
<td>0.15*</td>
<td>0.06</td>
</tr>
<tr>
<td>HOME Inventory score (out of 45)</td>
<td>0.33***</td>
<td>0.37***</td>
<td>0.22**</td>
</tr>
<tr>
<td>Mother’s knowledge score (^3) (out of 16)</td>
<td>−0.07</td>
<td>−0.04</td>
<td>−0.00</td>
</tr>
</tbody>
</table>

\(^1\) Values are Pearson’s correlation coefficients. *P < 0.05, **P < 0.01, ***P < 0.001. Eight of the 186 children refused to participate. Bayley III, Bayley Scales of Infant and Toddler Development III test; HOME, Home Observation for the Measurement of the Environment.

\(^2\) Child’s age was partialled in all analyses.

\(^3\) Values are based on a calculation of mothers’ estimates of children’s milestones in months.
example, Black et al. (14) provided zinc to small-for-gestational-age infants and found no effect on their mental development. The higher effects in the current study may be due to the provision of 22-element micronutrient fortification in vulnerable populations such as LBW children.

The choice of a 22-element nutritional supplement and the inclusion of nutrition education for intervention and control groups may be considered as another difference. In fact, many recent MMN studies were intentionally investigating the role of a single nutrient, such as zinc or iron, in comparison with other nutrients, rather than that of MMNs compared with nutrition education only as we implemented here. The effects of a 22-element MMN plus nutrition, health, and hygiene education may have produced a synergistic effect that is not found when supplements are offered alone. Many MMN interventions did not find effects on nutrition indicators and this may also explain the lack of developmental effects. The lack of effects on height, in particular, is consistent with the systematic review by Dewey and Adu-Afarwuah (36), which showed that micronutrient fortification of foods yielded weaker effects on height and weight than complementary foods. Our intervention group not only was administered 22-element micronutrients but also was provided with 35 contacts to discuss educational messages about nutrition, health, and hygiene. The education component may partly account for our findings, potentially sustaining the effect 4–10 mo after the intervention ended. Taken together, these findings suggest that LBW-T children in low-income countries may benefit most when they receive micro- and macronutrient supplements and intensive education; however, the specific combination of nutrients is not yet known.

We have no evidence to help explain the significant effects of a 22-element MNP on LBW-T children’s language development but not cognition. One possibility concerns the narrow optimal window for language development. Sound recognition, word meaning, and syntax develop in sequence in the first 24 mo. Better nutrition at this age might have made children more receptive to speech in the home, starting with sound recognition at 6–10 mo (37). This window of opportunity may remain open longer for cognitive development and the kind of problem-solving assessed by the Bayley may rely more on gradual learning. Another explanation may be that vulnerable populations are more delayed in language than cognition (38); however, it should be noted that this study included very LBW children. If LBW-T children are susceptible to similar language problems, then boosting their nutritional status may affect language more than cognition. Our data with LBW-T children showed that those in the control group attained significantly lower scores on the expressive language test than children in the intervention group, and those in the control group who were stunted scored significantly lower on the receptive language test than nonstunted children. Both explanations rely on the

### TABLE 3 Comparison of control (nutrition, health, and hygiene education) and intervention (MNP plus nutrition, health, and hygiene education) groups on Bayley III cognitive and language outcomes at 16–22 mo of age (n = 178)

<table>
<thead>
<tr>
<th>Scales of Infant and Toddler Development III test</th>
<th>MNP, multiple micronutrient powder.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cognitive</td>
<td>39–62</td>
</tr>
<tr>
<td>Standardized cognitive</td>
<td>3–15</td>
</tr>
<tr>
<td>Total receptive language</td>
<td>12–31</td>
</tr>
<tr>
<td>Standardized receptive language</td>
<td>3–15</td>
</tr>
<tr>
<td>Total expressive language</td>
<td>12–34</td>
</tr>
<tr>
<td>Standardized expressive language</td>
<td>3–15</td>
</tr>
</tbody>
</table>

Values are means ± SDs unless otherwise indicated. *Effect size was Cohen’s d.*

1 Values are means unless otherwise indicated. *P* values were calculated with a cluster-adjusted ANCOVA by using treatment as the fixed effect and the following covariates: child’s age (mo), length for age (Z-score), mother’s education (y), family assets, and Home Observation for the Measurement of the Environment Inventory scores. Eight of the 186 children refused to participate. Bayley III, Bayley Scales of Infant and Toddler Development III test; MNP, multiple micronutrient powder.

2 Effect size was Cohen’s d.

3 Standardized Bayley means, with a theoretical range of 0–19, are provided for comparison with raw Bayley scores.

#### FIGURE 2 Moderation analyses examining the effect of stunting (length-for-age Z-score < 2.00) on intervention (22-element multiple micronutrient powder plus nutrition, health, and hygiene education) vs. control group (nutrition, health, and hygiene education only) for raw receptive language scores (n = 178). Values are mean standardized receptive language scores for the interaction between intervention and stunting among 4 groups: control stunted (n = 41), control nonstunted (n = 41), intervention stunted (n = 48), and intervention nonstunted (n = 48). The interaction term (*P* < 0.006) was included after main effects and covariates (child’s age, mother’s education, Home Observation for the Measurement of the Environment Inventory, assets) were entered in a multiple linear regression. A simple main effects analysis was conducted separately on control and intervention subgroups.

*Significantly different from nonstunted children in the control group only, *P* < 0.05.*
notion that language development is vulnerable to developmental risks.

The current study is not without limitations. In the follow-up, we did not measure the blood concentration of micronutrients such as iron and iodine, which may be related to cognitive development. Children administered an MNP usually show improvements in hemoglobin and other iron indicators (39) that are maintained; however, they were not assessed here. Similarly, although the current study did examine weight and height, there was no difference between groups at 16–22 mo of age in either indicator. This lack of difference may account for somewhat weak effects. For example, diversity in diet may have been insufficient to maintain significant effects from the MNP on length and anemia that were demonstrated at 12 mo of age (40). We also did not examine mental development at baseline or in relation to the children’s earlier length, anemia status, or morbidity at 12 mo. The analyses for the current study included only contemporaneous correlates. Finally, the current study had no placebo group. The control group here received the same educational messages as the intervention group on nutrition, health, and hygiene.

The strengths of the study include an adequately powered sample size, high compliance with the nutrition fortification, a newer version of the Bayley test that assesses separate domains of language and cognition, and inclusion of a measure of psychosocial stimulation that is known to be associated with mental development. In addition, we examined the effects of a 22-element MNP intervention 4–10 mo after it ended. Our findings reveal that a 22-element MNP can benefit children’s expressive language and reduce the gap between stunted and nonstunted children’s receptive language. In conclusion, MNPs may offer one feasible solution to improve LBW children’s development in low-resource community settings.

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