Maternal Multiple Micronutrient Supplements and Child Cognition: A Randomized Trial in Indonesia

abstract

OBJECTIVES: We investigated the relative benefit of maternal multiple micronutrient (MMN) supplementation during pregnancy and until 3 months postpartum compared with iron/folic acid supplementation on child development at preschool age (42 months).

METHODS: We assessed 487 children of mothers who participated in the Supplementation with Multiple Micronutrients Intervention Trial, a cluster-randomized trial in Indonesia, on tests adapted and validated in the local context measuring motor, language, visual attention/spatial, executive, and socioemotional abilities. Analysis was according to intention to treat.

RESULTS: In children of undernourished mothers (mid-upper arm circumference <23.5 cm), a significant benefit of MMNs was observed on motor ability (B = 0.39 [95% confidence interval (CI): 0.08–0.70]; P = .015) and visual attention/spatial ability (B = 0.37 [95% CI: 0.11–0.62]; P = .004). In children of anemic mothers (hemoglobin concentration <110 g/L), a significant benefit of MMNs on visual attention/spatial ability (B = 0.24 [95% CI: 0.02–0.46]; P = .030) was also observed. No robust effects of maternal MMN supplementation were found in any developmental domain over all children.

CONCLUSIONS: When pregnant women are undernourished or anemic, provision of MMN supplements can improve the motor and cognitive abilities of their children up to 3.5 years later, particularly for both motor function and visual attention/spatial ability. Maternal MMN but not iron/folic acid supplementation protected children from the detrimental effects of maternal undernutrition on child motor and cognitive development. Pediatrics 2012;130:e536–e546

AUTHORS: Elizabeth L. Prado, PhD, Katherine J. Alcock, DPhil, Husni Muadz, PhD, Michael T. Ullman, PhD, and Anuraj H. Shankar, DSc, for the SUMMIT Study Group

SUMMIT Institute of Development, Mataram, Indonesia; Department of Psychology, Lancaster University, Lancaster, United Kingdom; University of California at Davis Program in International and Community Nutrition, Davis, California; Mataram University Center for Research on Language and Culture, Mataram, Indonesia; Georgetown University Brain and Language Laboratory, Department of Neuroscience, Washington, DC; and Department of Nutrition, Harvard University School of Public Health, Cambridge, Massachusetts

KEY WORDS: child development, cognitive development, international public health, maternal health, maternal nutrition, motor development, multiple micronutrient supplementation

ABBREVIATIONS: Hb—hemoglobin; IFA—iron/folic acid; MMN—multiple micronutrient; MUAC—mid-upper arm circumference; SUMMIT—Supplementation with Multiple Micronutrients Intervention Trial

WHAT’S KNOWN ON THIS SUBJECT: Micronutrients are essential for brain development during gestation and infancy. Few randomized trials of maternal multiple micronutrient supplementation during pregnancy and postpartum have examined child outcomes beyond the neonatal period or tested which cognitive domains show long-term effects.

WHAT THIS STUDY ADDS: Children of undernourished mothers given multiple micronutrients performed as well as children of well-nourished mothers in motor and visual attention/spatial ability at age 42 months; children of undernourished mothers given iron/folic acid showed 4- to 5-month delays in these abilities.
Micronutrients are necessary for brain development during gestation and infancy. These are important periods for the formation of the brain, laying the foundation for the development of cognitive, motor, and socioemotional skills throughout childhood and adulthood. Children with restricted development of these skills during early life are at risk for later neuropsychological problems, poor school achievement, low-skilled employment, and poor care of their own children, thus contributing to the intergenerational transmission of poverty. More than 200 million children aged <5 years in low- and middle-income countries, at a conservative estimate, are not reaching their developmental potential in these areas.

Sufficient micronutrient intake is especially important when mothers are pregnant and breastfeeding, which are periods of increased micronutrient needs and crucial periods for the brain development of the infant. The neural tube begins to form 16 days after conception and within 7 months takes on a form that resembles the adult brain. Micronutrients are necessary for many of the biological processes that drive this transformation, including neuron proliferation, axon and dendrite growth, synaptogenesis, and myelination. For example, in animal models, maternal vitamin B<sub>6</sub> deficiency results in decreased synaptic density in the neocortex, whereas maternal deficiency in either vitamin B<sub>6</sub> or zinc leads to reduced dendritic branching. Maternal deficiency in iron and vitamin B<sub>6</sub>, as well as gestational hypothyroidism, which can be caused by deficiencies in iodine and selenium, result in reduced myelination in the offspring. Few studies have examined the effects of maternal micronutrient deficiencies on brain development in humans.

Although the World Health Organization recommends distribution of iron/folic acid (IFA) supplements to pregnant women, provision of multiple micronutrients (MMNs), including those important for brain development such as vitamin B<sub>6</sub>, zinc, and iodine, may be more beneficial for mothers and their children. Three randomized trials have examined the effect of maternal MMN supplementation on motor and cognitive development in infancy. Two of these have reported benefits on Bayley Scales of Infant Development motor scores in children (age 7 months) of undernourished mothers in Bangladesh and children (age 6–18 months) of HIV-1-infected mothers in Tanzania. A third trial in China found a benefit of maternal MMN supplementation compared with IFA on Bayley Scales of Infant Development mental but not motor scores at 12 months of age. These somewhat mixed results suggest that maternal MMN supplementation may improve motor development, although perhaps only in children of mothers who are at particular risk (ie, with HIV-1 infection or low BMI), and may also benefit other cognitive abilities.

Only 1 study has examined the effect of maternal MMN supplementation in older children: a randomized trial in Nepal, which assessed a cohort of 7- to 9-year-old children. Children whose mothers had received 15 micronutrients during pregnancy scored higher on a test of executive function than those whose mothers had received vitamin A alone. However, this benefit was found for only 1 of 6 tests of motor and cognitive function. Children of mothers in this same study who received iron, folic acid, and vitamin A scored higher on 5 of 6 cognitive and motor tests than those whose mothers received vitamin A alone. In this study, children whose mothers received iron, folic acid, and vitamin A were not directly compared with those who received 15 micronutrients. In addition, this study used an MMN formulation that did not contain iodine, which is important for child motor and cognitive development, nor did it assess the specific impact on children of undernourished or anemic mothers. Additional data are needed to investigate whether long-term benefits of maternal MMN supplementation, over IFA alone, may be observed for children in other contexts or for the development of other cognitive and socioemotional skills. Analyses directly comparing the current UNICEF/World Health Organization/United Nations University MMN formulation with IFA, as reported here, are also important to inform maternal health policy.

We examined the effect of maternal supplementation with MMNs, compared with IFA, on motor and socioemotional skills, as well as several specific aspects of cognitive ability: language, attention (the ability to focus and sustain attention), visuospatial ability (the ability to perceive and mentally represent spatial relationships among objects), and executive function (cognitive self-regulation, such as planning, effortful control of attention, and inhibition of automatic responses). In addition, in prespecified analyses, we examined interactions between maternal supplement type and 2 indicators of maternal nutritional status likely to be related to poor child development: undernourishment at enrollment (mid-upper arm circumference [MUAC] <23.5 cm) and anemia at enrollment (hemoglobin [Hb] concentration <110 g/L).

**METHODS**

This study was conducted as part of the Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT). A detailed description of the design and procedures of SUMMIT has been published previously. SUMMIT was a double-blind, cluster-randomized trial conducted on the Indonesian island of Lombok from 2001 through 2004. Pregnant women throughout Lombok were enrolled in SUMMIT at prenatal care clinics held...
by local midwives. Written informed consent was obtained from all participants. Consenting women received a daily supplement throughout the duration of pregnancy and until 3 months postpartum. Midwives were randomly assigned to distribute either IFA or MMNs. The contents of the 2 supplements are presented in Table 1. All women who received prenatal care from the same midwife received the same supplement. All SUMMIT scientists and personnel, government staff, and participants were unaware of the allocation of MMNs and IFA. The study protocol was approved by the National Institutes of Health Research and Development of the Ministry of Health of Indonesia, the Provincial Planning Department of Nusa Tenggara Barat Province, and the Johns Hopkins Joint Committee on Clinical Investigation (Baltimore, Maryland). Analysis was according to intention to treat.

SUMMIT staff visited participants within 72 hours of enrollment to record baseline information, including MUAC and Hb concentration, which were used to classify mothers as undernourished or anemic, respectively, in stratified analyses. Because midwives had been previously randomized to distribute IFA or MMNs, this classification was independent of randomization. Additional data were also collected (see Supplemental Information). The follow-up sample was drawn from a random sample of 2369 women who provided blood samples both before and after supplementation.

**Follow-up Sample**

Figure 1 shows the trial profile. A total of 28 426 children were born live, with 26 228 being alive at 12 weeks postpartum after mortality and loss to follow-up. To power the study to detect a difference of 0.3 SD and adding 15% for potential attrition, we targeted 549 mothers, comprising all mothers who gave birth between September 24, 2003, and March 31, 2004, and who had their blood drawn both before and after supplementation. We were able to test children of 484 of these mothers, including 3 sets of twins, for a total of 487 children. Of the targeted participants, the proportion who were not tested did not differ between IFA (32 of 272) and MMN (33 of 277) (P = .957). Fourteen motor scores (5 IFA, 9 MMN), 8 visual attention/spatial scores (2 IFA, 6 MMN), and 11 executive function scores (4 IFA, 7 MMN) were missing because the child refused to attempt the tests.

All testing was conducted from April to September 2007 at the homes of the participants within 3 weeks of the day the child turned 42 months. Written informed consent was obtained from a parent. Ethical approval for the informed consent and research procedures for the follow-up study was obtained from the Lancaster University Ethics Committee and the Mataram University Ethical Research Committee.

**Developmental Tests**

Developmental tests were selected that assess specific abilities which develop during early childhood and are likely to be sensitive to nutritional influences. Research in maternal and child undernutrition in humans and animals suggests possible effects on motor development, language development, and nonverbal cognitive development, including visual attention, visuospatial ability, and executive function, as well as socioemotional development. Tests that assess each of these domains were adapted to the local language, culture, and setting in Lombok, and were evaluated for reliability and validity. A full description of the test selection criteria, adaptations, and the reliability and validity results is reported in Prado et al. The tests are described in Table 2.

**Additional Measures**

The following data were also collected at the time of child testing: an adapted version of the Home Observation for the Measurement of the Environment inventory, the child’s Hb concentration, and maternal depression. For details, see Supplemental Information.

**Statistical Analyses**

**Group Characteristic Comparisons**

First, we examined whether children whose mothers received MMNs and IFA were matched on the characteristics listed in Table 3. For the continuous variables, the difference was estimated in mixed effects models. A random effect of midwife code on intercept was included in all analyses because the randomization was allocated by midwife rather than by individual participant;
specification of this random effect accounts for variation between midwife clusters. For the categorical variables, the difference between groups was estimated by using generalized linear models, with midwife code as a repeated measure. For details, see Supplemental Information.

Calculation of Test Scores

For each test score (described in Table 1), z scores were computed on the basis of the distribution of our sample. The computation of z scores harmonized every test score to the same scale. This allowed us to compute composite domain scores as the average of each child’s test z scores from that domain, in the following domains: language development, Picture Vocabulary and Sentence Complexity z scores; socio-emotional development, socioemotional competence and problem z scores; executive function, Snack Delay and Windows z scores; and visual attention/spatial ability, Visual Search and Block Design z scores. For details, see Supplemental Information. For the motor scale, 9.4% of item scores were missing. These missing items were imputed by using the sequential regression imputation method described in Raghunathan et al. For details, see Supplemental Information. We additionally performed the analyses on motor scores by counting refused (missing) items as a failure, rather than using imputation, and found a similar pattern of results.

Effect of Maternal MMN Versus IFA

The effect of MMN supplementation on each domain score was estimated in mixed effects models with a fixed effect of supplement type and a random effect of midwife code. This model was estimated first with a fixed effect of supplement type as the only independent variable, and second, with fixed effects of supplement type and any variables from Table 3 that independently predicted each domain score. For a detailed description of covariate selection, see Supplemental Information. Because gestational age at birth (pre-term, full-term, or post-term) did not significantly predict any domain score, this variable was not included as a covariate.

To examine the effect on each domain score in children of mothers who were undernourished (MUAC <23.5 cm) at enrollment and mothers who were anemic (Hb <110 g/L) at enrollment, the interaction between each of these 2 variables and supplement type was (separately) added to the model. If this interaction was significant at the P < .1 level, the effect of MMNs was estimated for each subgroup.

RESULTS

The effect of MMN supplementation on the composite score for each developmental domain is reported in Table 4. The estimate (B) represents the unstandardized estimate of the difference in developmental scores between children of mothers who received MMNs and IFA, expressed as a fraction of the variation (SD) of the developmental score. For example, children of mothers who received MMNs scored 0.12 SD higher in motor development compared with those who received IFA (P = .253). Although this effect on motor development was significant when adjusting for the covariates (P = .036), it was not significant in the unadjusted analysis. No significant effects of MMNs were found in any other developmental domain.
suggesting that there were no robust effects of maternal MMN supplementation in the full group of children.

**Children of Undernourished Mothers**

The interaction between maternal supplement type and maternal undernutrition (MUAC <23.5 cm) was significant for motor development (B = 0.412; SE = 0.199; t(399) = 2.07; P = .039) and visual attention/spatial ability (B = 0.454, SE = 0.168, t(420) = 2.71, P = .007) but not for language, executive function, or socioemotional development.

In motor development, children of undernourished mothers who received MMNs scored 0.35 SD higher than those who received IFA (P = .044) (Table 5). In a group of children aged 30 to 55 months in Lombok tested to establish the developmental sensitivity of the tests,19 the estimate of the effect of age (in months) on the motor development score was 0.08, indicating that motor development increased –0.08 SD with each additional month of age. Thus, this effect of maternal MMN supplementation on motor development (0.35 SD) represents an advantage equivalent to

### TABLE 2 Motor, Cognitive, and Socioemotional Tests

<table>
<thead>
<tr>
<th>Domain/Test</th>
<th>Method and Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Development</td>
<td>The fine and gross motor scales were developed by selecting age-appropriate items (10 fine motor items and 10 gross motor items) from both the Bayley Scale of Motor Development42 and the Ages and Stages Questionnaire44, for example, “Jumps over a rope 20 cm high” and “Threads three beads on a string.” The motor score was calculated as the total number of items, out of 20, that a child performed successfully.</td>
</tr>
<tr>
<td>Fine and Gross Motor Development Scales</td>
<td>based on the British Picture Vocabulary Scale,44 the child was presented 50 items, each consisting of 4 pictures (1 target and 3 distracters) and a word spoken by the tester. The child was asked to point to the picture corresponding to the word. Item scores were summed for a total score.</td>
</tr>
<tr>
<td>Cognitive Development</td>
<td>based on the MacArthur-Bates Communicative Development Inventory—Level III,45 the child’s parent or another caregiver was asked 16 questions concerning the child’s expressive language ability. For example, the parent was asked, given an appropriate context, “Which one more closely resembles your child’s speech: ‘I’m using my bag’ or ‘Tas te kadu jauq robot’ (I’m using my bag to carry a robot)? A score of 0 was given for the less complex structure and a score of 1 for the more complex structure. These items were adapted to the Sasak language based on transcripts of child speech.19 For each test, item scores were summed for a total score.</td>
</tr>
<tr>
<td>Language Ability</td>
<td>based on the British Ability Scale46 and the Wechsler Preschool and Primary Scale of Intelligence—Third Edition,47 the child was presented 7 shapes made with wooden blocks and was asked to build a copy of each. Thirty seconds were allowed per attempt. Children who failed on the first attempt were given a second attempt, only for the first 4 items. Children were scored on the average amount of time per correct item completed, which was then reciprocal transformed, reversing the score to match the direction of the other scores (higher is better).</td>
</tr>
<tr>
<td>Sentence Complexity Scale</td>
<td>based on the Brief Infant-Toddler Social and Emotional Development Scales43; for example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Visual Attention</td>
<td>based on aspects of both the British Ability Scale46 and the Wechsler Preschool and Primary Scale of Intelligence—Third Edition,47 the child was presented 50 items, each consisting of 4 pictures (1 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Language Ability</td>
<td>based on aspects of both the British Ability Scale46 and the Wechsler Preschool and Primary Scale of Intelligence—Third Edition,47 the child was presented 50 items, each consisting of 4 pictures (1 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Block Design Test</td>
<td>based on the Max-Art B and C and other children’s needs. For example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Visual Search Test</td>
<td>based on the NEPSY Developmental Neuropsychological Assessment visual search subtest.48 In each of 2 items, the child was shown an array of pictures and asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Executive Function</td>
<td>based on the Max-Art B and C and other children’s needs. For example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Snack Delay Test</td>
<td>based on the Max-Art B and C and other children’s needs. For example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Windows Test</td>
<td>based on the Max-Art B and C and other children’s needs. For example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Socioemotional Development</td>
<td>based on the Max-Art B and C and other children’s needs. For example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
<tr>
<td>Socioemotional Development Scale</td>
<td>based on the Max-Art B and C and other children’s needs. For example, “Does not make eye contact” (0 target and 3 distracters) and a word spoken by the tester. The child was asked to point to every instance of a target picture in the array, while the tester circled each picture the child indicated. The score was calculated as the number of hits (number of targets correctly indicated) minus the number of false alarms (number of distracter pictures incorrectly indicated).</td>
</tr>
</tbody>
</table>
∼4.5 months of age. No difference in motor scores was found in children of mothers who were not undernourished during pregnancy. This finding suggests that the effect of MMNs on motor development observed over all children in the adjusted analysis (Table 4) was due to this effect in children of undernourished, rather than well-nourished, mothers.

In visual attention/spatial ability, children of undernourished mothers who received MMNs scored 0.35 SD higher than those who received IFA (P = .011) (Table 5). Children of mothers who were not undernourished during pregnancy did not show this advantage. The effect of age in months on this score, in

<table>
<thead>
<tr>
<th>TABLE 3 Group Characteristic Comparisons of the Preschool Follow-up Sample Who Received IFA and MMNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Baseline maternal age, y</td>
</tr>
<tr>
<td>Baseline maternal height, cm</td>
</tr>
<tr>
<td>Mean compliance (percentage of supplements consumed)</td>
</tr>
<tr>
<td>Maternal cognitive z score</td>
</tr>
<tr>
<td>Maternal mood score at cognitive testing</td>
</tr>
<tr>
<td>Baseline maternal Hb concentration</td>
</tr>
<tr>
<td>Baseline Hb concentration, g/L</td>
</tr>
<tr>
<td>HOME inventory score</td>
</tr>
<tr>
<td>Child's hours of sleep in the 24 hours before testing</td>
</tr>
</tbody>
</table>

All baseline measures were taken within 72 hours of enrollment. Maternal cognitive and mood scores were taken from Prado et al.39

a Comparisons using mixed effects models for continuous variables (t is reported) and generalized linear models for categorical variables (z is reported).

b The socioeconomic index was derived from a survey administered at enrollment to determine whether participants owned 12 household items. Subsequently, we discarded 6 items with correlations with the total score of <0.1. Removing these items improved the internal consistency of the index from Cronbach’s a = 0.41 to 0.57. The 6 remaining items (owned a radio; a television; a refrigerator; a bike; a motorbike; and a small sales business, such as selling snacks, commonly operated out of the home) were summed for a total score.

~4.5 months of age. No difference in motor scores was found in children of mothers who were not undernourished during pregnancy. This finding suggests that the effect of MMNs on motor development observed over all children in the adjusted analysis (Table 4) was due to this effect in children of undernourished, rather than well-nourished, mothers.

In visual attention/spatial ability, children of undernourished mothers who received MMNs scored 0.35 SD higher than those who received IFA (P = .011) (Table 5). Children of mothers who were not undernourished during pregnancy did not show this advantage. The effect of age in months on this score, in
the aforementioned sample of children aged 30 to 55 months, was 0.07, indicating that this score increased by \sim 0.07 SD with each month of age. Therefore, the effect of MMNs in children of undernourished mothers represents an advantage equivalent to \sim 5 months of age. Both the effects on motor and visual attention/spatial ability in children of undernourished mothers were slightly stronger in the analyses adjusting for the covariates (B = 0.39 and B = 0.37, respectively).

The mean z score for each domain in children of mothers who received IFA and MMNs stratified on the basis of the mother’s MUAC is presented in Fig 2. Children of undernourished mothers who received IFA scored substantially lower in motor development (mean: -0.28) and visual attention/spatial ability (mean: -0.35) than all other groups (mean: 0.01–0.10). Children of undernourished mothers who received MMNs had scores (mean: 0.07 for motor ability and 0.01 for visual attention/spatial ability) similar to children of mothers who were not undernourished in either supplement group (mean: 0.01–0.10). This finding suggests that maternal MMN supplementation protected children of undernourished mothers from negative developmental effects of the mother’s poor nutritional status during pregnancy.

### TABLE 4 Effect of MMNs on Motor, Cognitive, and Socioemotional Domain Scores

<table>
<thead>
<tr>
<th>Domain</th>
<th>Adjusted for Cluster Randomization</th>
<th>Adjusted for Cluster Randomization and Other Covariates That Independently Predicted Each Domain Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Estimate (95% CI) P</td>
<td>n Estimate (95% CI) P</td>
</tr>
<tr>
<td>Motor development</td>
<td>473 0.12 (-0.08 to 0.32) 0.253</td>
<td>425 0.19 (0.02 to 0.37) 0.036</td>
</tr>
<tr>
<td>Language development</td>
<td>487 0.00 (-0.20 to 0.19) 0.971</td>
<td>380 0.07 (-0.11 to 0.25) 0.465</td>
</tr>
<tr>
<td>Visual attention/spatial ability</td>
<td>479 0.08 (-0.09 to 0.24) 0.355</td>
<td>424 0.07 (-0.08 to 0.22) 0.342</td>
</tr>
<tr>
<td>Executive function</td>
<td>476 -0.06 (-0.21 to 0.09) 0.427</td>
<td>385 -0.04 (-0.19 to 0.11) 0.654</td>
</tr>
<tr>
<td>Socioemotional development</td>
<td>487 -0.02 (-0.16 to 0.12) 0.777</td>
<td>410 0.00 (-0.15 to 0.15) 0.981</td>
</tr>
</tbody>
</table>

The estimate of the effect of MMNs represents the difference in scores between children of mothers who received MMNs and IFA, expressed as a fraction of the variation (SD) of the score. Positive estimates indicate that those who received MMNs scored higher than those who received IFA. The interaction term P value represents the P value associated with the interaction between maternal supplement type and the stratification variable (mother’s MUAC or Hb). CI, 95% confidence interval.

**Children of Anemic Mothers**

The interaction between maternal supplement type and maternal anemia (Hb <110 g/L) was significant at the P < .1 level for visual attention/spatial ability (B = 0.292, SE = 0.157, t(469) = 1.88, P = .063) but not for any other domain score.

Children of anemic mothers who received MMNs scored 0.23 SD higher in visual attention/spatial ability than those who received IFA, an effect which approached significance in the unadjusted analysis (P = .055) and was significant in the adjusted analysis (B = 0.24, P = .030) (Table 5). This effect size represents an advantage equivalent to \sim 3 months of age. Children of mothers who were not anemic during pregnancy did not show a benefit of maternal MMN supplementation on visual attention/spatial ability.

### DISCUSSION

In a randomized trial in Indonesia that examined the effects of maternal MMN supplementation, compared with IFA, on the motor, cognitive, and socioemotional abilities of children at age 42 months, the following results were found. No significant effects were found for children overall, except in the adjusted analysis on motor development. Stratified analysis showed that this
Effect on motor development was found only in children of mothers who were undernourished during pregnancy and was equivalent to ∼4.5 months of age. Maternal MMN supplementation also yielded advantages in visual attention/spatial ability in 2 subgroups of children: children of mothers who were undernourished during pregnancy, equivalent to ∼5 months of age, and children of mothers who were anemic during pregnancy, equivalent to ∼3 months of age. These findings have several implications.

First, these results demonstrate that adequate maternal micronutrient intake is necessary for intact brain development, a conclusion that in the past has largely depended on animal models. Although acute maternal deficiencies in certain micronutrients are known to result in severe neurologic impairment (eg, maternal iodine deficiency resulting in cretinism), the effect of mild to moderate micronutrient deficiencies during pregnancy in humans has not yet been clarified. The finding that children of undernourished mothers who received IFA performed at substantially lower motor and cognitive levels compared with those who received MMNs and compared with children of well-nourished mothers (Fig 2) suggests that supplementation with IFA alone is insufficient to protect against negative long-term developmental effects of maternal undernutrition. The MMN supplement in the current study contained iodine, zinc, and vitamin B6, all of which are important for brain development. Maternal iodine supplementation has been found to improve motor and cognitive development in several studies. Maternal zinc supplementation has been found to improve muscle mass in 12-month-old infants, which could lead to improved motor development, although improvements in motor development have not been observed in 2 other studies of maternal zinc supplementation. Thus, adequate intake of other micronutrients in addition to iron/folic acid during pregnancy and lactation seems to be important for healthy motor and cognitive development.

Second, the finding that MMN supplementation benefited these children’s motor and cognitive abilities in undernourished mothers is consistent with previous evidence that maternal MMN supplementation can provide other important advantages, such as reductions in low birth weight and infant mortality 3 months postpartum, and suggests that these advantages extend beyond gestational and early infant health outcomes. The finding is also consistent with the positive findings of the 3 previous studies that examined the effect of MMN supplementation on Bayley Scales of Infant Development mental and motor scores and provides important additional elements, such as the evaluation of multiple domains of early child development and the careful adaptation of the tests to the local setting. Perhaps most importantly, whereas those studies focused on infants (up to age 18 months), the current study examined children at 42 months of age. Infant development scores are generally poor predictors of later cognitive abilities; in contrast, those scores of children ages 3 to 7 years predict later outcomes such as school achievement, which in turn leads to higher skilled employment and higher wages in adulthood. The fact that we found a benefit of MMN supplementation

FIGURE 2
Mean z score in each developmental domain for children of mothers who received IFA and MMNs stratified on the basis of the MUAC of the mother. Error bars show the SEM.
in visual attention/spatial ability is intriguing because focusing and sustaining attention are important skills for school success. Moreover, attention measured before and during elementary school has been found to predict school achievement up to 5 years later. Thus, the results obtained here suggest that maternal MMN supplementation might have much longer-term advantages for children of undernourished and anemic mothers.

Third, the finding that the motor and cognitive benefits were observed primarily in the children of mothers who were undernourished or anemic during pregnancy is consistent with previous studies that have observed a particular benefit of MMN supplementation in these subgroups on infant survival, maternal cognition, and infant motor development, although not on birth weight. Together, these findings suggest that micronutrient deficiency may be especially problematic among these subgroups, and that these mothers and their children particularly benefit from MMN supplementation during pregnancy and postpartum in certain important outcomes. Given that some studies have found no differences between maternal MMN and IFA supplementation on neonatal infant mortality or on cognitive performance at age 7 to 9 years, this highlights the importance of examining effects in subgroups of mothers who are particularly likely to benefit from MMN supplementation.

We found no effects on language, executive, or socioemotional skills. One limitation of this study was that the children were tested at an age in which a wide variation in performance is normal. For example, because a wide variation in language ability falls within a normal range at age 3 years, it may be difficult to detect effects in language development at this age. Another limitation was that the tests of executive function in the current study primarily assessed inhibition ability (in both the Snack Delay and Windows tests) and, to some extent, task switching (in the Windows test). In later childhood, it becomes easier to assess other aspects of executive function, including planning and task monitoring, which might be more sensitive to maternal MMN supplementation. A third limitation was that our measure of socioemotional development relied on parent report rather than direct assessment of the child, which may also be more sensitive to effects of maternal MMN supplementation.

CONCLUSIONS

Our findings suggest that, in a population such as that examined here in Indonesia, maternal MMN supplementation compared with IFA supplementation can improve the motor and cognitive abilities of children as late as 3.5 years, in particular when women are undernourished or anemic during pregnancy, and especially for motor function and visual attention/spatial ability. The loss of developmental potential in early childhood is a critical problem in low- and middle-income countries. The findings suggest that providing MMN supplements to mothers during pregnancy and lactation, particularly to those who are undernourished or anemic, is an effective intervention to address this loss and to promote healthy motor and cognitive development in children.

ACKNOWLEDGMENTS

The SUMMIT Study Group designed and executed the SUMMIT study. We acknowledge the substantial contribution of Dr Abas Jahari in the support and completion of the study. Sri Hartini, Astri Hidayanti, Siti Nurul Hikmah, Baqi Elfa Ismayani, Atik Rahmawati, and Fitriati conducted pilot testing, test adaptation, and data collection. Nurhafni, Indah Qoriana, Rosmawarti, and Nuniks I. Gayatri provided administrative support. Farhiyah, Nurawati, and Maryati transcribed child speech samples to validate the parent-reported language measure.

REFERENCES

9. Mørré DM, Kirksey A, Das GD. Effects of vitamin B-6 deficiency on the developing


41. Bayley N. Bayley Scales of Infant Development. 2nd ed. San Antonio, TX: Psychological Corporation; 1993


Address correspondence to Elizabeth L. Prado, PhD, SUMMIT Institute of Development, Kantor Bappeda Provinsi Nusa Tenggara Barat, Lantai 2, Jalan Flamboyan No 2, Mataram, NTB, Indonesia. E-mail: elprado@ucdavis.edu and Katherine Alcock, DPhil, Department of Psychology, Lancaster University, Bailrigg, Lancaster, LA1 4YF, United Kingdom. E-mail: k.j.alcock@lancaster.ac.uk

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Support for this project was provided by the Allen Foundation, a National Science Foundation Graduate Research Fellowship, the Turner Foundation, UNICEF, the Centre for Health and Human Development, and the United States Agency for International Development–Indonesia (grant 497-G-00-01-00001-00). The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Maternal Multiple Micronutrient Supplements and Child Cognition: A Randomized Trial in Indonesia

Elizabeth L. Prado, Katherine J. Alcock, Husni Muadz, Michael T. Ullman and Anuraj H. Shankar

*Pediatrics* 2012;130;e536; originally published online August 20, 2012; DOI: 10.1542/peds.2012-0412

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: /content/130/3/e536.full.html</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary Material</td>
<td>Supplementary material can be found at: /content/suppl/2012/08/15/peds.2012-0412.DCSupplemental.html</td>
</tr>
<tr>
<td>References</td>
<td>This article cites 38 articles, 10 of which can be accessed free at: /content/130/3/e536.full.html#ref-list-1</td>
</tr>
<tr>
<td>Citations</td>
<td>This article has been cited by 3 HighWire-hosted articles: /content/130/3/e536.full.html#related-urls</td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): <strong>Nutrition</strong> /cgi/collection/nutrition_sub</td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml</td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: /site/misc/reprints.xhtml</td>
</tr>
</tbody>
</table>
Maternal Multiple Micronutrient Supplements and Child Cognition: A Randomized Trial in Indonesia
Elizabeth L. Prado, Katherine J. Alcock, Husni Muadz, Michael T. Ullman and Anuraj H. Shankar

Pediatrics 2012;130:e536; originally published online August 20, 2012;
DOI: 10.1542/peds.2012-0412

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/130/3/e536.full.html