Three-month nutritional supplementation in Indonesian infants and toddlers benefits memory function 8 y later\(^1\)\(^-\)\(^3\)

Ernesto Pollitt, William E Watkins, and Mahdin A Husaini

ABSTRACT  Does short-term supplementary feeding during infancy and childhood have long-lasting effects? In 1986, 334 children aged 6–60 mo living on rural tea plantations in West Java, Indonesia, participated in a 3-mo randomized trial to test the effects of a dietary supplement providing \(\approx 1672 \text{ kJ (400 kcal)}\) energy/d, with about the same nutrient density as local foods. We returned to the same communities in 1994 and enrolled 231 (125 supplemented, 106 control) of the original subjects in a follow-up study of the long-term effects of supplementation. We assessed these subjects by using several measures: anthropometry, iron status, information processing, Peabody Picture Vocabulary Test, word fluency, and an arithmetic test. The supplemented group showed no differences from those in the control group. However, when the analysis was limited to subjects who had received the supplement before the age of 18 mo (\(n = 73\)), the supplemented children performed better than control children on the Sternberg test of working memory (decision time intercept: probe absent, \(P = 0.002\); probe present, \(P = 0.053\)). After considering possible confounders, we concluded that the supplementation during infancy was responsible for the difference. This finding shows that supplementation can have long-lasting effects on a specific domain if the child receives it at the appropriate stage of development. Am J Clin Nutr 1997;66:1357–63.

KEY WORDS  Nutritional supplementation, infant development, child development, cognition, memory, infants, toddlers, Peabody Picture Vocabulary Test, Indonesia

INTRODUCTION

Numerous studies have investigated the effects of nutritional status during infancy and early childhood on cognition in late childhood or adolescence, including natural experiments such as the Dutch “hunger winter” (1) and controlled experiments conducted in Guatemala (2), Colombia (3), Costa Rica (4), and Chile (5). Moreover, much work has shown that children aged < 3 y with poor nutritional status are most vulnerable to growth stunting and disease. The investigators assumed that children with better nutritional status, because of food supplements or other sources, would perform better in later life, particularly if they received the supplements in early infancy. Results of the controlled experiments have generally supported this assumption. For example, in Guatemala (2), early supplementary feeding during gestation and for at least the first 2 y of life enhanced subjects’ performance at ages 11–24 y on tests of numeracy, general knowledge, vocabulary, and reading comprehension.

The experimental treatment in these studies generally lasted > 6 mo, except for experiments with preterm (\(< 1850 \text{ g}\)) infants, who consumed banked breast milk or formula for \(\approx 1\) mo of intensive care after delivery. Those who had received breast milk performed better on an intelligence test at ages 7.5–8 y than did subjects who received preterm formula (6).

The subjects in our study participated as infants and toddlers in a supplementation study that lasted for 3 mo in 1986–1987 (7, 8; henceforth referred to as the original study). This paper reports the results of a follow-up study conducted in 1994–1995, when these children were of school age.

SUBJECTS AND METHODS

Location

The original and follow-up studies were both conducted on government-owned tea plantations near Pengalengan, 50 km southeast of Bandung, the capital of West Java, Indonesia, at 1500–1800 m above sea level. Virtually all subjects were Sundanese, the predominant ethnic group in West Java, who spoke Sundanese and Indonesian (the official language taught in schools). All subjects were Muslim and often learned Arabic in religious schools. The subjects’ families were all employed by the tea plantations, which had established daycare centers for the employees’ children. These centers were used to contact and recruit subjects. (For more information on the original study and the communities, see references 7–9.)

Study design

The original study was a randomized field trial in which children aged 6–60 mo at the daycare centers were given a snack (777–897 kJ per snack) twice daily for 3 mo to supplement the meals normally provided by the daycare center. The snacks, which included a variety of locally prepared foods

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Received February 19, 1997.

Accepted for publication May 22, 1997.

(rice, rice flour, wheat flour, bread, cassava, potatoes, sweet potatoes, coconut milk, refined sugar, brown sugar, and edible oil), were analyzed for their macronutrient content.

In this study it was not possible to randomly assign at the individual level because it was unreasonable to give food to some and not to other children in the same room. The best solution, therefore, was to randomize daycare centers into two groups and statistically control the variability of all 20 daycare centers. This strategy provided the best picture of the treatment effects. We collected complete data for 334 children before and after the 3-mo trial. Of the original 334 subjects, 231 were contacted again in 1994; most of the others had moved with their families away from the plantation. On average, the 103 subjects who were lost to follow-up did not differ from the 231 remaining subjects in age, sex distribution, group (treatment or control) distribution, anthropometric measurements, hemoglobin, or developmental scores in the original study. The parents of every potential subject consented to participate in the follow-up study, which was approved by the human subjects protocol committees of the authors’ institutions.

Follow-up study

Field personnel blinded to the treatment status of the subjects conducted the following assessments.

Anthropometry

We used standard methods to measure height, weight, head circumference, and skinfold thicknesses (10).

Hematology

We measured hemoglobin using the cyanmethemoglobin procedure, serum iron and total-iron-binding capacity using kits from Boehringer Mannheim (Mannheim, Germany), and free erythrocyte protoporphyrin in blood specimens using an automatic ZP hematoassaymeter (model 206; Boehringer Mannheim, Amsterdam).

Cognitive tests

The children individually took computerized tests drawn from the Cognitive Abilities Tests (11), which assess elementary cognitive processes. The testers were Sundane-speaking psychologists, graduates of a university in Bandung. We used a touch screen so that subjects could touch the computer screen directly rather than using the keyboard. The monitor was mounted 30° from the horizontal in a specially constructed frame so that the subjects’ hands were comfortably positioned directly over the screen. The tests measured 1) simple and choice reaction time, 2) Sternberg working memory scanning (12) (Figure 1), 3) probe recall, and 4) tachistoscopic threshold. In the reaction time test, one to eight empty boxes appear on the screen and subjects are asked to touch as rapidly as possible the box that is illuminated. With the Sternberg working memory scanning, subjects are shown a memory set of one to four figures and are then asked to decide whether the probe is part of the memory set. In the probe-recall test, six figures and a probe appear successively on the screen and subjects are then asked to recall the position of the probe figure among the set of six. In the tachistoscopic threshold test, two figures are shown in very rapid succession and subjects must decide whether the figures are identical.

Emotionality

We administered the tachistoscopic threshold test—a difficult test for children of this age—as a stressor and used a time sampling technique to observe and code the motor behavior of each child during testing. At 30-s intervals the testers noted the subjects’ physical movements, facial expressions, or sounds indicative of increased emotionality.

Peabody Picture Vocabulary Test

We administered individually a Sundanese version of form B of the Peabody Picture Vocabulary Test (13), in which subjects are shown a plate with four pictures, given a word, and then asked to point to the appropriate picture.

Arithmetic test

In collaboration with local psychologists, we developed an arithmetic test appropriate for children of this age. We reduced the original set of 100 questions to 50 and rearranged them in order of difficulty so that the early questions could be answered by all and the later questions answered by few or none. After two rounds of pretesting, we administered the revised version in the classroom, giving the children 30 min to answer the 50 questions. The internal validity of the test was confirmed by the expected improvement in scores for each grade.

Socioeconomic status

The original study assumed homogeneity of the communities and did not evaluate socioeconomic status. In the follow-up study we assessed socioeconomic status to determine whether there were differences between the early and the later groups. This assessment showed that most families lived under comparable conditions during both of the study periods, thus confirming our original assumption of homogeneity. By calculating composite scores for family assets and housing quality, we found no differences between the groups for these composite variables, nor for years of schooling for the father and mother or for total family income. Therefore, we made no socioeconomic status adjustments.
Statistical analysis

The goal of this study was to compare performance by group to test the effects of early supplementation. We examined the data to determine whether they met the assumptions of parametric statistics, and if they did not, we used log-transformations to improve the normality and homoskedasticity of distributions. Because of the unit of randomization in the original study was the daycare center, we nested the daycare centers within treatment groups for the first level of analysis. We also tested for covariance, using individuals as the unit of analysis, with adjustments for age, sex, and (where appropriate) tester. SAS software (version 6.10; SAS Institute Inc, Cary, NC) was used for the analysis.

Although the original study was designed to test the hypothesis that all supplemented children would perform better than control subjects, we tested whether the results varied depending on the age of the child when supplementation began. We thus analyzed the data using various age groups (eg, 12, 18, 24, or 36 mo at the beginning of study).

RESULTS

Original study

We first used the daycare centers to test for treatment effects, but found no clear effects for any of the cognitive tests. This finding was expected because of the limited degree of freedom available for comparison among clusters of institutions. After analyzing all subjects, as well as the subgroups who had entered the original study at different ages, we found no significant differences between the supplemented and control groups in any of the outcome variables (n = 231). However, those who had entered the original study when aged <18 mo had significant differences from the rest of the sample, and thus we present the data for these subjects. (The following data, unless specified otherwise, refer to these younger children.)

The original sample consisted of 66 supplemented (65%) and 36 control children; a similar proportion (63%) was found in the follow-up sample (46 supplemented, 27 control children). The sex ratio in the follow-up sample (49% girls) was comparable with that of the original sample (46% girls). There were no significant differences between groups at baseline in age, sex, anthropometry (height, weight, and head circumference), hemoglobin, or Mental Scales on the Bayley Scales of Mental and Motor Development (14). There were, however, baseline differences in the Bayley Motor Scales favoring the control group (not shown). Baseline dietary intake at the daycare center was not significantly different between the two groups. However, energy and protein intakes increased in the supplemented group during the intervention (Table 1); the amount of energy in the supplements corresponded to the difference between habitual energy intake (as determined in a baseline survey) and the energy intake recommended in Indonesia. We do not have solid data on dietary intakes outside of the daycare center during the experiment, and so we do not know to what extent, if any, the supplement replaced food intake outside of the daycare center. However, the greater weight gain in the supplemented than in the control subjects during the 3 mo of supplementation showed that the supplement increased total intake (7).

Follow-up study

There were no anthropometric or hematologic differences between groups (Table 2). On average, the children in the two groups were stunted (mean height-for-age z score: -2.14); however, the mean weight-for-height z score (-0.10) shows that wasting was not common.

With one exception, none of the cognitive or emotional outcomes discriminated between groups. The exception was the Sternberg test (Figure 1), which showed that supplementation during infancy led to improved working memory 8 y later. Because the daycare center effect was not significant, we analyzed further data using the individual as the unit of analysis. Significant (P < 0.05) differences of ≤ 0.15 s were seen in decision time when the probe was absent (Figure 2A) and significant or nearly significant differences (P < 0.06) of

<table>
<thead>
<tr>
<th>Nutrient and group</th>
<th>Before supplementation</th>
<th>After supplementation</th>
</tr>
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<tbody>
<tr>
<td>Energy (kJ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemented</td>
<td>1249 ± 103 [34]</td>
<td>2476 ± 98 [38]</td>
</tr>
<tr>
<td>Control</td>
<td>1149 ± 116 [22]</td>
<td>1139 ± 91 [19]</td>
</tr>
<tr>
<td>Plant protein (g)</td>
<td></td>
<td></td>
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<tr>
<td>Supplemented</td>
<td>2.82 ± 0.33 [26]</td>
<td>4.39 ± 0.64 [30]</td>
</tr>
<tr>
<td>Control</td>
<td>3.29 ± 0.65 [15]</td>
<td>2.08 ± 0.56 [13]</td>
</tr>
<tr>
<td>Fat (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemented</td>
<td>5.64 ± 0.48 [34]</td>
<td>10.06 ± 0.48 [36]</td>
</tr>
<tr>
<td>Control</td>
<td>5.66 ± 1.44 [22]</td>
<td>3.91 ± 0.41 [19]</td>
</tr>
<tr>
<td>Vitamin A (µg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemented</td>
<td>227.7 ± 42.3 [31]</td>
<td>844.2 ± 89.1 [38]</td>
</tr>
<tr>
<td>Control</td>
<td>180.9 ± 63.9 [21]</td>
<td>138.6 ± 19.2 [19]</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemented</td>
<td>1.69 ± 0.26 [34]</td>
<td>3.20 ± 0.16 [38]</td>
</tr>
<tr>
<td>Control</td>
<td>1.52 ± 0.16 [22]</td>
<td>1.35 ± 0.13 [19]</td>
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<tr>
<td>Calcium (mg)</td>
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<tr>
<td>Supplemented</td>
<td>106.24 ± 10.32 [34]</td>
<td>142.08 ± 10.89 [38]</td>
</tr>
<tr>
<td>Control</td>
<td>67.77 ± 11.22 [22]</td>
<td>74.26 ± 7.67 [19]</td>
</tr>
</tbody>
</table>

\(^7 x \pm SE; n in brackets. Subjects lost to follow-up were not included.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supplement group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at follow-up (mo)</td>
<td>111.98 ± 0.70 [46]</td>
<td>112.22 ± 0.85 [27]</td>
</tr>
<tr>
<td>Age at treatment (mo)</td>
<td>12.70 ± 0.55 [46]</td>
<td>12.63 ± 0.76 [27]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>120.42 ± 0.72 [46]</td>
<td>121.40 ± 1.17 [27]</td>
</tr>
<tr>
<td>Height-for-age z score</td>
<td>-2.23 ± 0.10 [46]</td>
<td>-2.07 ± 0.19 [27]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>22.31 ± 0.43 [46]</td>
<td>22.71 ± 0.56 [27]</td>
</tr>
<tr>
<td>Weight-for-age z score</td>
<td>-1.67 ± 0.09 [46]</td>
<td>-1.57 ± 0.13 [27]</td>
</tr>
<tr>
<td>Weight-for-height z score</td>
<td>-0.11 ± 0.15 [45]</td>
<td>-0.10 ± 0.13 [26]</td>
</tr>
<tr>
<td>Duration of schooling (y)</td>
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<td></td>
</tr>
<tr>
<td>Father</td>
<td>4.10 ± 0.23 [39]</td>
<td>4.13 ± 0.28 [23]</td>
</tr>
<tr>
<td>Mother</td>
<td>3.40 ± 0.22 [45]</td>
<td>3.42 ± 0.34 [26]</td>
</tr>
<tr>
<td>Income (rupiah)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>111 936 ± 13 983 [39]</td>
<td>107 656 ± 12 742 [23]</td>
</tr>
<tr>
<td>Mother</td>
<td>84 779 ± 5 724.2 [39]</td>
<td>79 872 ± 8 652 [23]</td>
</tr>
<tr>
<td>Household income (rupiah)</td>
<td>185 508 ± 15 189 [45]</td>
<td>178 338 ± 15 935 [27]</td>
</tr>
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</table>
similar magnitude when the probe was present (Figure 2B). There were no group differences in the slope coefficients (Figure 2) but there were significant differences in the intercept: with the probe, the supplemented group was 0.11 s faster ($P = 0.053$, adjusting for age, sex, and tester) than the control subjects; with no probe they were 0.15 s faster ($P = 0.002$).

We also examined the mean decision-time intercepts by group and age of supplementation (Figure 3; children were grouped into 6-mo cohorts, except for the last two groups, which were 1-y cohorts to keep the sample sizes approximately the same). For the control children, the speed of decision time decreased as age increased, a finding the same as from other studies of ours (WE Watkins, JR Cruz, E Pollitt, unpublished observations, 1997; S Cueto, E Jacoby, E Pollitt, unpublished observations, 1997). However, for the supplemented children there appeared to be a bell-shaped curve: after 18 mo of age the supplemented and control children had similar times, but before 18 mo of age the supplemented children were as fast as children > 2 y older. Mean decision time (Spearman $r = 0.99$) showed high intratetest reliability and, although we did not assess test-retest reliability with this population, we found reasonably high test-retest correlations ($> 0.6$) (WE Watkins et al, unpublished observations, 1997) in our previous work with a similar population.

**DISCUSSION**

The key finding of this study was that administration of a high-energy supplement to infants and toddlers for 3 mo led to greater scanning speed of working memory 8 y later. This effect was seen only in those who had received the feeding supplements at an early age (usually before 18 mo of age; the minimum age of entry into the study was 6 mo) and did not extend to the other outcomes tested. Supplementation before 18 mo of age increased children's working memory speed considerably over that of their control peers; those supplemented before 12 (mean age at follow-up: 8.93 y) or 18 mo of age were as fast as the oldest age group supplemented (now =12.5 y old) (Figure 3).

Because the children were not stratified by age before being assigned to treatment in the original study, we were cautious in interpreting the results. Before we could accept a causal relation and discuss its possible mechanisms and importance, we considered alternate explanations.

1) The subgroups were dissimilar at baseline. A comparison of baseline data between follow-up and dropout subjects and between supplemented and control subjects showed that the two groups had similar ages, anthropometric indexes, hemoglobin concentrations, and developmental scores before the intervention began.

2) The effect was due to a confounder that preferentially affected the supplemented group but not the control group over the previous 8 y. We had no systematic information on the history of the children from the end of the original study to the beginning of the follow-up. This gap was important because the unit of randomization was the daycare center whereas the analysis was based on potentially confounding differences between the histories.

**FIGURE 2.** Mean (± SEM) Sternberg decision time by block number and treatment groups: ●, supplemented children, $n = 46$; ■, control children, $n = 27$. A, probe absent; B, probe present. The $P$ value represents the difference between the two groups, adjusted for age, sex, and tester.
of the communities and those of the respective daycare centers. However, although this explanation is plausible, its validity is not likely because the plantations have no records of significant demographic or environmental changes in any of the communities or daycare centers. Moreover, we found no evidence of changes in socio-economic status or in most follow-up outcomes measured. Ironically, our failure to find differences in most of the outcomes bolsters the validity of the outcome in which we did find a difference. If we had found many differences after such a short intervention with a relatively low-quality supplement, we might have suspected that the groups had not been equivalent at the start of the study or had had different experiences in the intervening 8 y.

3) The result was a chance finding because of the large number of comparisons made. Following the advice of Rothman (15), we did not control statistically for the number of comparisons made. As outlined in Table 2, we looked at 7 background variables and 26 outcome variables. Normally we would not need to consider all of these comparisons, because several of the variables are closely linked (eg, weight and weight-for-age z score). What this high number of comparisons does is increase the likelihood that the sample from the two populations (which, according to the null hypothesis, are truly alike) would show differences in one or two outcomes below the commonly used significance threshold of 0.05. However, the $P$ values we report for the decision times in the working memory test are generally $<0.05$ (as low as 0.002), making a type I error unlikely. Furthermore, we should remember that statistics are merely a guide to inference, and that no $P$ value, no matter how small, can exclude the possibility that our finding is merely a result of chance. Instead, we should first consider the biological plausibility of our observation, followed by the statistical probability that it is real, and by these criteria we believe that what we observed was biologically plausible and not a result of chance.

4) The effect was caused by the extra attention given to those who received the supplement. Some field trials testing the effects of giving food (for which there cannot be an identical placebo) give extra attention to the control children to exclude the possibility that it is attention and not food producing the effect. We cannot definitively exclude this possibility, but it seems unlikely that attention alone could have had an influence lasting 8 y.

5) The interaction between age and supplementation is related to the age of testing. The children who were supplemented before 18 mo of age were $\approx$9 y old at the time of testing, and those supplemented after 18 mo of age were, for the most part, 10–12 y old when tested. A possibility that our study design cannot, strictly speaking, exclude is that the interaction we observed between age and supplementation was a result of the age of testing, not of the age of supplementation. If this were true, all supplemented children would do better than control subjects when tested at 9 y of age, but this difference would
disappear when they were tested after age 10 y. Our explanation, in contrast, was that the children supplemented at the later age and who showed no differences in performance at ages 10–12 y would also have scored the same as control subjects when tested at age 9 y, whereas the children supplemented earlier, who scored better at age 9 y, would continue to do better than control subjects even when tested after the age of 10 y.

Although the study design cannot exclude the possibility that age of testing determines the extent of a developmental effect of earlier supplementation, we maintain that age of supplementation is the more likely determinant. We know of no evidence that the ability of the Sternberg test to discriminate is subject to a later cutoff age. However, because there are definite age threshold and cutoff effects in childhood interventions, we believe that the age of supplementation explained the results better than did the age of testing.

Having established that there are good reasons for inferring a causal relation between the supplement and the improved speed of working memory, we can consider possible mechanisms. To address this issue we must consider the biological plausibility of the findings and whether memory was indeed affected. In light of our present knowledge of early malnutrition and later performance in experimental animals (16) and human populations (17), the findings reported in this paper are biologically plausible. For example, Pollitt et al (2) found that a protein-energy intervention in utero that continued through the first 2 y of life benefited performance on a wide range of cognitive tests administered during adolescence. This effect was also observed when the intervention was initiated from age 2 y onward. However, the breadth and extent of the effects were significantly less in this latter group than those observed in the group that was supplemented before age 2 y.

Was memory between the groups distinct? Our findings represent a coherent set of data that fit a theoretical model of memory. However, the experimental design was not flawless and because there was no external criterion to validate the findings, it is reasonable to question whether the results were due to chance or reflected an effect on other processes such as attention and reaction time or simply a response bias.

The Sternberg test is designed to assess scanning in working memory when retrieval is nearly perfect. In our study the subjects' performance was not perfect, but the number of recall errors was similar in both groups, suggesting that the respective demands on working memory were equivalent. This equivalence allows for a fair comparison and analysis of the differences observed in test performance in the context of Sternberg's theory. First, the two groups showed similar increments in decision time as a function of block size; therefore, the two slopes for each probe condition should be treated as parallel lines. Second, the differences in intercepts and decision time between groups were consistent for the different test conditions: regardless of whether the probe was present or absent, the control children reacted more slowly.

To address the issue of particular effects in memory, it is important to note that the slopes of the two groups had a nearly exact fit with Sternberg's theoretical expectations and empirical results regarding exhaustive memory search (12, 18). We therefore used this agreement as a criterion to validate the claim that the test taps memory scanning and that the intercepts represent the time the brain takes first to encode the probe and then to compare the probe with items in memory to determine whether the probe is present or absent. Accordingly, our conclusion was that the result of the early nutritional supplement was an increment in the overall speed of retrieval, i.e., the experimental group was faster than the control group.

This study initially focused on a high-energy supplement; however, we could draw no conclusions on any one nutritional factor, given that the subjects consumed a variety of locally prepared snack foods containing various nutrients (a research weakness that is a programmatic strength because it shows that locally produced foods can improve outcomes). Although our primary interest in this study was the long-term effects of undernutrition on memory, we found the Sternberg test to be sensitive to relatively short-term effects, such as whether the subjects were dewormed (19) or whether they had eaten breakfast (20).

Ideally, a physiologic mechanism would describe neurologic developments before the age of 18 mo that are related specifically to memory and that would suffer irreversible damage from a nutritional deficiency. For this mechanism to explain our data, the age of 18 mo should serve as an approximate cutoff. However, current findings suggest that such mechanisms are largely from animal studies and it is difficult to precisely match stages of development between animals and humans.

Myelination, which increases the speed of neural transmission, serves as a crude marker of regional neurologic development (21) and is significantly correlated with other neurologic and behavioral developments (22). It occurs from gestation through the age of 7 y in humans (23). Studies in rats have shown that general undernutrition, particularly iron deficiency, can lead to irreversible deficits in brain myelination (24); reduced myelin is found even with mild undernutrition (25). In rats the critical period appears to be 8–14 d (24); the comparable period in humans, based on the period of peak growth, appears to be 6–18 mo (26). In terms of timing and the nature of the nutritional deficiency, it seems plausible that the unsupplemented children may have suffered deficits in myelination, but if this was so, we do not know why we saw an effect only in working memory and not in the other tests of cognitive function.

Another plausible mechanism is permanent alterations in the structure and neurophysiology of the hippocampus, an area of the brain thought to be essential for short-term but not permanent memory (27). Experiments with laboratory animals have shown alterations in the hippocampus, which are not amenable to rehabilitation; prenatal undernutrition has the strongest effect (28) but postnatal undernutrition (reduced milk intake) has resulted in impaired working memory in adult rats (29). The effects seen in rats are subtle, with only certain tests revealing differences between adequately nourished and undernourished rats. Therefore, we should not be surprised by the subtlety of our results.

Work with animals has suggested that altered cognitive performance after a period of undernutrition may actually result from increased emotionality rather than from impaired cognitive function (16). We attempted to test this hypothesis in our subjects by observing their physical movements, facial expressions, and sounds made while taking a particularly difficult test. These behaviors were not different between groups, suggesting that emotions did not play a role in the differences
observed in working memory. However, the observed behavioral equivalence between groups provides at least modest support for such a claim because neither the construct nor the normative validity of the method used to assess emotional response was established.

The apparent importance of timing in determining whether supplementation has an effect on cognition supports the assumption that there are critical periods in development. This notion has been somewhat discredited (16) because the use of global measures of cognition has not been successful in identifying critical periods beyond which the organism can no longer overcome a deficit. However, because global outcomes by definition are measures of many individual processes, these outcomes may not be sensitive enough to reveal changes in any one of the processes. Our data suggest that the critical period for the neural developments required for faster retrieval from working memory is before 18 mo of age.

We gratefully acknowledge the support of the Nestlé Foundation and the devoted assistance of Abas Jahari, Nina Triana, and Dewi Purnomosari.

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