A micronutrient-fortified seasoning powder reduces morbidity and improves short-term cognitive function, but has no effect on anthropometric measures in primary school children in northeast Thailand: a randomized controlled trial

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ABSTRACT

Background: Reductions in iodine and zinc deficiencies and improvements in hemoglobin were achieved from a micronutrient-fortified seasoning powder consumed in school lunches by children in northeast Thailand.

Objective: The objective was to determine whether fortification with 4 micronutrients in a school lunch results in changes in children’s growth, morbidity, and cognitive function compared with no fortification.

Design: In a randomized controlled trial of 569 children aged 5.5–13.4 y from 10 schools, we compared the efficacy of a seasoning powder fortified with or without 5 mg Fe, 5 mg Zn, 50 μg I, and 270 μg vitamin A per serving consumed with a school lunch 5 d/wk. Here we report on results of the secondary functional outcomes.

Results: The groups were comparable concerning compliance and loss to follow-up. The intervention had no statistically significant effect on anthropometric measures over 31 wk, but reduced the incidence of respiratory-related illnesses [rate ratio (RR): 0.83; 95% CI: 0.73, 0.94], symptoms of runny nose (RR: 0.80; 95% CI: 0.70, 0.92), cough (RR: 0.80; 95% CI: 0.66, 0.96), and diarrhea (RR: 0.38; 95% CI: 0.16, 0.90). For the visual recall test, those in the fortified group recalled 0.5 more items (95% CI: 0.1, 0.9) than did the controls. There were no statistically significant differences between groups in the results of the digits forward and backward tests or in school grades at the conclusion of the 2 semesters.

Conclusion: The beneficial effects on morbidity and visual recall over a short period, in addition to some biochemical improvements, highlight the potential of this micronutrient-fortified seasoning powder supplied in a school lunch. This trial was registered at clinicaltrials.gov as ACTRN12605000341628. Am J Clin Nutr 2008;87:1715–22.

INTRODUCTION

Reducing the prevalence of micronutrient deficiencies is a high priority for many health policy makers in the governments of developing countries. Impairments in growth, immune competence, and cognitive function have been reported among school-age children with deficiencies of iron, zinc, vitamin A, and iodine (1). Such adverse health consequences can lead to reductions in both productivity and intellectual potential in adulthood (2).

Several micronutrient supplementation trials in Thailand have examined functional health outcomes such as growth, morbidity, and cognitive function (3–8). Most of these Thai trials have focused on single micronutrients (eg, iron, iodine, vitamin A, or zinc), and the results have been mixed. Methodologic and clinical heterogeneity, including variability in participants (eg, coexistence of multiple micronutrient deficiencies; 9), may account for some of these inconsistencies.

In response to concerns about coexisting micronutrient deficiencies among schoolchildren in developing countries, targeted multiple micronutrient fortification strategies using biscuits (10) or beverages (11–14) have been investigated. This is a relatively new approach, and only a few studies have examined their efficacy on functional health outcomes as well as on biochemical indexes. In some cases, improvements in growth (11–13), cognitive function (10, 14), and reductions in diarrhea and respiratory-related illnesses have been reported (10).

Biochemical results from this randomized controlled trial (RCT), including the primary outcome anemia, have been reported previously (15). We demonstrated that a seasoning powder fortified with 4 micronutrients and incorporated into a school-lunch program reduced the prevalence of iodine and zinc deficiencies and improved the hemoglobin status of primary school children in northeast Thailand, although there was no intervention effect for anemia or serum ferritin. Although improvements in these biochemical outcomes are promising, improvements in functional health outcomes are also of key importance. In this publication we report the efficacy of the

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2 Supported by the Micronutrient Initiative Fund, the University of Otago Research Fund, and the Institute of Nutrition, Mahidol University.
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intervention on outcomes of anthropometric measures, morbidity, and cognitive function.

SUBJECTS AND METHODS
Study population and design
Details of the RCT design, including inclusion and exclusion criteria, are described in an earlier publication (15). Briefly, this RCT was conducted in the 10 poorest subdistricts of Trakan Phutphon district, Ubon Ratchathani province, northeast Thailand between August 2002 and March 2003. The school with the largest roll in each of the 10 subdistricts was invited to participate in the RCT.

Eligible primary school children from each of the 10 schools whose parents or guardians had given written informed consent were stratified within each school into 4 strata: girls grades 1–3, boys grades 1–3, girls grades 4–6, and boys grades 4–6. Fifteen children from each stratum were randomly selected, except for strata with <15 children when all children were selected, yielding a total of 569 children. In families with more than one eligible child, only one child was randomly selected. The study protocol was explained in detail to each participating school and family and was approved by the Human Ethics Committees of Mahidol University, Thailand, and the University of Otago, New Zealand.

The children enrolled in this RCT were randomly assigned to either the fortified or unfortified group by a biostatistician in New Zealand (JEM) who had no involvement in the recruitment process; details are given by Winichagoon et al (15). One group received a school lunch on each school day for 31 wk, which contained a seasoning powder (monosodium glutamate, salt, sugar, hydrolyzed vegetable protein, and dried meat powder) fortified with 4 micronutrients at the level of one-third of the Recommended Daily Intake set by the Thai Food and Drug Administration for food labeling purposes; the other group received an identical school lunch containing unfortified seasoning powder. Briefly, the fortificants consisted of iron (5 mg as H-reduced elemental iron), vitamin A (270 µg as palmitate), iodine (50 µg as potassium iodide), and zinc (5 mg as zinc sulfate) per serving. The fortified and unfortified school lunches were indistinguishable in color, taste, and appearance and were varied according to a biweekly rotating menu that included rice and noodles, twice and thrice weekly, respectively, each with a serving of meat and vegetables on top. Soups were served separately in plastic bags. The lunches were prepared in a central location and dispatched to the children on each school day in plastic boxes containing standardized portion sizes. Children ate their respective lunches under the supervision of a form teacher, who recorded on a pictorial chart whether the child ate “all,” “more than half,” “half,” “less than half,” or “none” of the school lunch. These amounts were later translated into fractions: 1.0, 0.75, 0.5, 0.25, and 0, respectively, were summed for each child and used to calculate the mean amount of school lunch eaten per intervention per child, as described previously (15).

At baseline, sociodemographic, health, and selected anthropometric outcomes were measured, together with nonfasting blood samples and casual urine samples for biochemical assessment. At follow-up, biochemical (15), anthropometric, and cognitive outcomes were measured. Morbidity was measured throughout the period of follow-up.

Anthropometric measures
Details of the collection of weight, height, and midupper arm circumference measurements are provided by Thurlow et al (9). Triceps and subcapular skinfold thicknesses were measured on the right side to the nearest 0.1 mm with precision calipers (Lange; Beta Technology Inc, Cambridge, MD) using standardized techniques (16). Knee height was measured on the right leg by using a knee height measuring device (KHMD) (InterSciences Development Associates Inc, Philadelphia, PA) and a standardized procedure (17). All anthropometric measurements were taken in triplicate by the same trained anthropometrist using calibrated equipment while the children were wearing light clothing and no shoes. The mean of the 2 closest measurements was calculated and used as the outcome. At the end of the standardization period, intraexaminer technical errors of the anthropometric measurements (TEMs) were close to the corresponding reference values recommended by Frisancho (18). The EpilInfo program [version 6.0; Centers for Disease Control and Prevention (CDC), Atlanta, GA] and National Center for Health Statistics/CDC/World Health Organization growth reference data (19) were used to calculate z scores for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) for boys 90–145 cm and girls 90–137 cm.

Morbidity
At baseline, morbidity data were based on self-reported infection status (respiratory, diarrhea, and parasite status) obtained through personnel interviews with the parents or caregivers of the children. At this time, parents or guardians were also informed about the standardized check list that would be used by the form teachers to record the morbidity data throughout the RCT and were requested to inform the form teacher if their child had experienced any of the symptoms on the standardized check list. The symptoms recorded were respiratory-related illnesses (runny nose, cough, and sore throat), fever, skin rash, other illnesses, and diarrhea-related illnesses (diarrhea, vomiting, nausea, and stomach pain). Diarrhea was defined as the passage of loose or liquid stools and a high stool frequency (ie, ≥3 stools/d). A morbidity episode was defined as an event of morbidity symptoms with 3 illness-free days between events. If a child was absent from school, then the reason for the absence was obtained retrospectively from the mother, guardian, or child and recorded on the standardized checklist by the teacher. Morbidity data were collected on each school day by the form teacher for a maximum of 214 weekdays and also retrospectively for 60 weekend days and 5 public holidays.

Cognitive function tests
The battery of cognitive tests were chosen to test short-term learning, memory, and attention span and included the digit span subset from Wechsler’s Intelligence Scale for Children III (WISC-III) (20) and a visual recall task modified from Seshadri and Gopaldas (21). Both tests required minimal adaptation for use in the Thai culture and are widely used. The test protocols were translated into the northeast Thai dialect, pretested, and then refined and tested again in 2 schools in a district not involved in the study.

The order of administration of the tests was randomly assigned to avoid any order effect. Tests were administered to the children individually by trained examiners who were experienced with
children. Testing was performed in an empty room. Examiners were trained to create a stress-like situation for the tests by using statements such as “it is important that you do your best,” “your teachers are interested in these test results,” and “parents might want to know your scores too” according to Trenham (22). We hypothesized that children with suboptimal micronutrient status would have more difficulties coping with stress than would those whose micronutrient status had improved.

Throughout the tests, examiners maintained a formal and serious tone and reinforced the importance of “doing ones best.” For the digit span, both digits forward (maximum n = 9) and digits backward (maximum n = 8) were administered by reading the digits at the rate of one per second. Children were instructed to recall increasingly longer strings of digits, first forwards, and then a second set backwards. Each forward and backward test had 2 trials, and each trial was discontinued after failure. The individual scores for the digits forward and digits backward were the sum of item scores on digits forward (maximum score: 16 points for 2 trials) and digits backward (maximum score: 14 points for 2 trials), respectively.

For the visual recall test, children examined 15 miniature objects placed on a school desk for 1 min, after which the objects were covered and the child was asked to recall as many objects as possible within a maximum of 2 min. All the objects were familiar to the children and included a toothbrush, key, scissors, mandarin, coin, picture of a temple, stone, slice of bread, comb, watch, box of milk, sock, spoon, picture of birds, and a pencil. The objects were placed on the desk in the same position and order for every trial according to a paper template. A child scored 1 point for each item correctly identified, with a maximum score of 15 points for the 15 items. School grades (as percentages) for Thai, Mathematics, English, and Science for each participant were also collected from the school records over the 2 semesters of the academic year.

Statistical analysis

The primary outcome for this trial was anemia, defined as a hemoglobin concentration <115 g/L and <120 g/L for those children between 5 and 12 y of age and ≥12 y of age, respectively. Results of this outcome and other secondary biochemical outcomes, along with the statistical methods used and the trial sample size justification were presented previously (15). The present publication reports the results of additional secondary, anthropometric, cognitive, and morbidity outcomes.

Multiple linear regression models were used to estimate the effectiveness of the intervention for continuous outcomes. In these models, the design strata (age in months, sex, and school) were included as explanatory variables. School was included as a fixed effect (23). For anthropometric outcomes, the baseline measure of the outcome was additionally included as an explanatory variable. Adjustment for baseline of the outcome using a fixed effect (23). For anthropometric outcomes, the baseline measure of the outcome was additionally included as an explanatory variable. Adjustment for baseline of the outcome using a fixed effect (23).

Negative binomial regression was used to estimate the effectiveness of the intervention for morbidity episodes. Negative binomial regression was used in preference to Poisson regression because there was evidence of overdispersion in morbidity episodes. These models were adjusted for the design strata. However, some outcomes had limited events; therefore, adjustment was made only for sex and age. Two additional models were fitted for the outcomes: respiratory- and diarrheal-related illnesses. These included an interaction term between intervention and age (months) to test whether age modified the intervention effect. These additional analyses were not prespecified and should be viewed as hypothesis generating.

Duration of respiratory-related illness, runny nose, and cough were compared between groups using multiple linear regression. Only these morbidity outcomes were analyzed because there were a reasonable number of children who experienced these illnesses. For each child, an average duration of illness was calculated as the total number of days with the illness divided by the number of episodes of the illness. These outcomes were natural log transformed to reduce heteroscedasticity of the residuals. From these models, the exponential of the estimated intervention effect provides a ratio of the geometric mean of the outcome in the fortified group to that in the unfortified group. Participants were analyzed as randomized. No imputation was performed. All statistical analyses were carried out in STATA SE version 9.2 (25).

RESULTS

At baseline, there were no clinically important differences in sociodemographic, health status (Table 1), or anthropometric (Table 2) variables. The majority of the head of the households and caregivers of the children in both groups had little education beyond primary school, and rice farming was their main source of income. One-third of the children in each group were reported to use vitamin/mineral supplements.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fortified (n = 283)</th>
<th>Unfortified (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td>111 ± 20.7</td>
<td>110 ± 20.2</td>
</tr>
<tr>
<td>Girls [n (%)]</td>
<td>144 (50.5)</td>
<td>143 (50.4)</td>
</tr>
<tr>
<td>High school education of caregiver [n (%)]</td>
<td>28 (9.9)</td>
<td>30 (10.6)</td>
</tr>
<tr>
<td>Head of household [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (12.4)</td>
<td>40 (14.1)</td>
</tr>
<tr>
<td>Has high school education [yes]</td>
<td>43 (15.2)</td>
<td>43 (15.2)</td>
</tr>
<tr>
<td>Employed in agriculture [yes]</td>
<td>265 (93.7)</td>
<td>257 (90.8)</td>
</tr>
<tr>
<td>Family income ≤30 000 Thai baht [yes]</td>
<td>144 (50.9)</td>
<td>155 (54.8)</td>
</tr>
<tr>
<td>Morbidity [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used vitamin/mineral supplements [yes]</td>
<td>23 (8.1)</td>
<td>12 (4.2)</td>
</tr>
<tr>
<td>Parasite infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99 (35.0)</td>
<td>102 (36.0)</td>
</tr>
<tr>
<td>No</td>
<td>82 (29.0)</td>
<td>67 (23.7)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>102 (36.0)</td>
<td>114 (40.5)</td>
</tr>
<tr>
<td>Treated for parasites in the ‘ill’/last year [yes]</td>
<td>172 (60.8)</td>
<td>167 (59.0)</td>
</tr>
<tr>
<td>Illness in the past month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea [yes]</td>
<td>16 (5.7)</td>
<td>24 (8.5)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>119 (42.1)</td>
<td>139 (49.1)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (7.8)</td>
<td>27 (9.5)</td>
</tr>
</tbody>
</table>

1 Values are x ± SD; n in parentheses.
2 Total n = 285.
3 Total n = 284.
4 Includes iron, multivitamin and minerals, vitamin A, and vitamin C.
Anthropometric measures

There were no statistically significant intervention effects for any of the anthropometric outcomes (Table 3).

Morbidity

Morbidity data were collected for a median of 207 days, with an interquartile range of 205 to 210 days, for both the fortified and unfortified groups. Incidence rates and rate ratios (RRs) for respiratory- and diarrhea-related illnesses and their symptoms are presented in Table 4. There was evidence of a lower incidence rate of respiratory-related illnesses, and symptoms of runny nose and cough for those receiving the fortified food. While there was no statistically significant reduction in the incidence of sore throat, the RR was of similar magnitude to that observed for the other respiratory-related symptoms.

The incidence of fever, skin rash, and other (primarily including headache and constipation) symptoms were not statistically significantly different between groups.

The incidence rate of diarrheal-related illnesses, and symptoms of vomiting, nausea, and stomach pain were not statistically significant between groups. However, the incidence of stomach pain was higher in those receiving the fortified food (RR: 0.38; 95% CI: 0.16, 0.90). Although there was evidence to suggest a reduction in the incidence of respiratory-related illness and symptoms of respiratory illness (runny nose and cough), there were no statistically or clinically important differences in the duration of these illnesses between groups (Table 5).

Post hoc, analyses were carried out to investigate whether the intervention effects for respiratory- and diarrheal-related illnesses were modified by age. We hypothesized that the intervention effect may be greater for younger children than for older children because older children have improved acquired and innate immunity and thus may be less susceptible to infectious illnesses. There was no evidence that age modified the intervention effect for respiratory-related illnesses (P = 0.568). From the statistical model, the rate of respiratory-related illnesses in the intervention group for children aged 10 years was 0.81 (95% CI: 0.70, 0.94) times that in the control group. For children aged 8 years, the RR was 0.85 (95% CI: 0.73, 0.98). The ratio of these RRs was

### Table 2

Selected anthropometric characteristics of the fortified and unfortified groups at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fortified (n = 283)</th>
<th>Unfortified (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>127.5 ± 10.44</td>
<td>127.3 ± 10.07</td>
</tr>
<tr>
<td>Knee height (mm)</td>
<td>389.4 ± 37.07</td>
<td>387.4 ± 35.03</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25.0 ± 7.24</td>
<td>24.9 ± 6.95</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.1 ± 2.16</td>
<td>15.1 ± 2.20</td>
</tr>
<tr>
<td>Arm circumference (cm)</td>
<td>18.2 ± 2.53</td>
<td>18.2 ± 2.52</td>
</tr>
<tr>
<td>Subscapular (cm)</td>
<td>5.4 ± 2.51</td>
<td>5.7 ± 2.85</td>
</tr>
<tr>
<td>Triceps (cm)</td>
<td>7.1 ± 3.02</td>
<td>7.1 ± 3.14</td>
</tr>
<tr>
<td>Sum of skinfolds thicknesses (cm)</td>
<td>12.5 ± 5.38</td>
<td>12.8 ± 5.78</td>
</tr>
</tbody>
</table>

### Table 3

Estimated intervention effects for anthropometric outcomes at follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fortified (n = 280)</th>
<th>Unfortified (n = 283)</th>
<th>Difference in means²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>131.3 ± 10.77</td>
<td>131.1 ± 10.31</td>
<td>0.10 (−0.05, 0.25)</td>
</tr>
<tr>
<td>Knee height (mm)</td>
<td>402.7 ± 37.49</td>
<td>400.8 ± 35.22</td>
<td>0.11 (−0.40, 0.62)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>27.0 ± 8.03</td>
<td>27.1 ± 7.72</td>
<td>−0.06 (−0.24, 0.13)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.3 ± 2.24</td>
<td>15.5 ± 2.38</td>
<td>−0.07 (−0.16, 0.02)</td>
</tr>
<tr>
<td>Arm circumference (cm)</td>
<td>18.7 ± 2.63</td>
<td>18.8 ± 2.72</td>
<td>−0.08 (−0.17, 0.01)</td>
</tr>
<tr>
<td>Subscapular skinfold thickness (cm)</td>
<td>5.4 ± 2.25</td>
<td>5.6 ± 2.76</td>
<td>−0.06 (−0.19, 0.08)</td>
</tr>
<tr>
<td>Triceps skinfold thickness (cm)</td>
<td>7.2 ± 2.89</td>
<td>7.4 ± 3.18</td>
<td>−0.11 (−0.31, 0.10)</td>
</tr>
<tr>
<td>Sum of skinfold thicknesses (cm)</td>
<td>12.6 ± 4.96</td>
<td>13.0 ± 5.72</td>
<td>−0.16 (−0.46, 0.14)</td>
</tr>
</tbody>
</table>

¹ Only children who had both baseline and follow-up measurements of the variables were used in the calculation of means.

² Estimate of the intervention effect adjusted for design strata: age (mo), sex, school (10 schools), and baseline of the outcome.
Respiratory related
participated because some children had already left on vacation
only 254 in the fortified group and 253 in the unfortified group
Cognitive function
1.07 (95% CI: 0.64, 1.77).
with the control group was 0.92 (95% CI: 0.58, 1.47) and 0.87
estimated to be 4% higher in the fortified group after adjustment for design
strata. However, because the 95% CI contains the null value of 1.0, there is
no evidence of a difference between groups.

There was evidence of a statistically significant intervention
effect for visual recall. Children in the fortified group recalled on
average 0.5 (95% CI: 0.1, 0.9) more items than did those in the
unfortified group (Table 6). There were no statistically signifi-
cant differences between groups for the digits forward and back-
ward tests.
There were no statistically significant differences between
groups for the average grade for any of the school subjects in
either semester (Table 6). The confidence limits of the interven-
tion estimates ruled out any important differences. The largest
percentage difference between groups for any of the subjects was
only 0.40% (95% CI: –1.37%, 2.17%) for English in semester 1.

Cognitive function
For the cognitive function tests administered at follow-up,
only 254 in the fortified group and 253 in the unfortified group
participated because some children had already left on vacation
(n = 57), were sick (n = 1), or were mentally disabled (n = 1).

TABLE 5
Estimates at follow-up of intervention effect for average duration of
morbidity in days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fortified</th>
<th>Unfortified</th>
<th>Ratio of geometric means</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory related</td>
<td>2.8 (221)</td>
<td>2.6 (236)</td>
<td>1.04 (0.93, 1.16)</td>
<td>0.528</td>
</tr>
<tr>
<td>Runny nose</td>
<td>2.7 (213)</td>
<td>2.6 (224)</td>
<td>1.00 (0.89, 1.13)</td>
<td>0.946</td>
</tr>
<tr>
<td>Cough</td>
<td>2.2 (156)</td>
<td>2.2 (168)</td>
<td>0.99 (0.85, 1.16)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

1 All values are geometric means; n in brackets.
2 Estimate of intervention effect adjusted for design strata: age (mo),
   sex, and school (10 schools).
3 Includes one or more of runny nose, cough, or sore throat.
4 The average duration of respiratory-related illnesses is, on average,
estimated to be 4% higher in the fortified group after adjustment for design
   strata. However, because the 95% CI contains the null value of 1.0, there is
   no evidence of a difference between groups.

DISCUSSION
Anthropometric measures and morbidity
We observed no statistically significant effect of the interven-
tion for the anthropometric outcomes, despite a reduction in the
number of morbidity episodes and prevalence of zinc and iodine
deficiencies (15). Other studies using micronutrient-fortified
beverages have observed statistically significant improvements
in height (12), weight, BMI (11–13), and arm circumference (11,
13). However, these earlier studies have not reported estimates of
effectiveness making direct comparison difficult.
Several factors probably contributed to the absence of a sta-
tistically significant effect on growth. First, few children (ie,
10%) were stunted at baseline. Second, the intervention was of a
relatively short duration, especially given the age of our partic-
ipants and hence their slower growth rate relative to preschoolers
(26). Third, there were fewer potentially growth-limiting micro-
nutrient fortificants in our Thai seasoning powder (n = 4) than in
the beverages (n = 5 or 6). Certainly, at recruitment, intakes of
≥3 other growth-limiting micronutrients not supplied by the
fortified seasoning powder—calcium, phosphorous, and riboflavin—were low (27–32), exacerbated by deficits in energy (28), maybe partly induced by impaired appetite and taste acuity associated with zinc deficiency (15, 28). Indeed, low energy intakes could be another growth-limiting factor, although anthropometric measures often respond to micronutrients alone, even among children with suboptimal energy intakes (33). Finally, variability in the anthropometric outcomes was probably greater among children with suboptimal energy intakes (33). Finally, variability in the anthropometric outcomes was probably greater than in earlier studies because we included children experiencing the pubertal growth spurt in stature. This occurs earlier among Asians than among other population types (26, 34).

Very few micronutrient fortification trials among schoolchildren have examined morbidity, except for the South African Biscuit Study, in which fewer school days due to respiratory- and diarrhea-related illnesses were missed in the fortified than in the unfortified group (10). Because of our intervention design, we could not attribute the reduction in morbidity to individual micronutrients in the fortified seasoning powder. However, because zinc has a key role in enhancing immune function (35) and potential antiviral properties (36) and because we observed a significant reduction in zinc deficiency (15), the zinc fortificant was most likely responsible for the reduced morbidity reported here. In addition, the form of the zinc fortificant (ie, zinc sulfate) could not explain the nonsignificant increase in stomach pain incidence. The serious tone used to describe the 2 cognitive test protocols, might have improved its discriminatory power of the visual recall. Certainly, the latter might have been less stressful because they involved the immediate recall of strings of digits that gradually increased in length, thus allowing the child to ease into the task. In contrast the visual recall required the child to immediately remember a series of digits that gradually increased in length, thus allowing the child to ease into the task. In contrast, the visual recall required immediate undivided focus and attention that, coupled with the time limit imposed, might have improved its discriminatory interaction and/or combined effect of the 4 micronutrients on immune function cannot be excluded.

There is likely to have been measurement error in the morbidity data collection because details of illnesses were recorded by the teachers from parental reports and were not confirmed by a medical professional. This measurement error is unlikely to have been differential between groups, but could have reduced the precision of the intervention estimates, resulting in wider CIs and/or bias toward the null.

**Cognitive function and educational achievement**

The visual recall and digit span subtests of WISC-III are tests of fluid intelligence that measure short-term learning and memory and attention span. The respondents’ performance on these tests tends to deteriorate when they feel anxious and less capable of coping with the immediate situation (40), as might occur when micronutrient status is compromised. All domains of cognitive functioning are impaired by micronutrient deficiencies (6, 41–43) and sensitive to changes in micronutrient status among schoolchildren (21, 43–46). Of the 2 cognitive tests, only the visual recall performance was statistically significantly improved by the micronutrient fortification, even though the digit span subtests also measure the same domains of cognitive functioning. The visual recall subtests also measure the same domains of cognitive functioning. The serious tone used to describe the 2 cognitive test protocols, but not the digit span subtests, may have enhanced the discriminatory power of the visual recall. Certainly, the latter might have been less stressful because they involved the immediate recall of strings of digits that gradually increased in length, thus allowing the child to ease into the task. In contrast the visual recall required immediate undivided focus and attention that, coupled with the time limit imposed, might have improved its discriminatory interaction and/or combined effect of the 4 micronutrients on immune function cannot be excluded.

<table>
<thead>
<tr>
<th></th>
<th>Fortified(^1)</th>
<th>Unfortified(^1)</th>
<th>Estimate (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive function</strong></td>
<td></td>
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</tr>
<tr>
<td>Visual recall(^2)</td>
<td>10.0 ± 2.30 (254)</td>
<td>9.4 ± 2.50 (253)</td>
<td>0.5 (0.1, 0.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Digits forward(^4)</td>
<td>9.3 ± 2.25 (254)</td>
<td>9.1 ± 1.94 (253)</td>
<td>0.1 (–0.2, 0.5)</td>
<td>0.417</td>
</tr>
<tr>
<td>Digits backward(^4)</td>
<td>3.2 ± 1.56 (254)</td>
<td>3.3 ± 1.53 (253)</td>
<td>–0.1 (–0.3, 0.2)</td>
<td>0.642</td>
</tr>
<tr>
<td><strong>School grades</strong></td>
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</tr>
<tr>
<td>Thai</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Semester 1</td>
<td>72.1 ± 10.95 (282)</td>
<td>71.7 ± 11.67 (284)</td>
<td>0.35 (–1.35, 2.05)</td>
<td>0.685</td>
</tr>
<tr>
<td>Semester 2</td>
<td>73.6 ± 11.56 (282)</td>
<td>73.2 ± 12.25 (284)</td>
<td>0.34 (–1.39, 2.06)</td>
<td>0.700</td>
</tr>
<tr>
<td>Math</td>
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</tr>
<tr>
<td>Semester 1</td>
<td>68.3 ± 11.78 (282)</td>
<td>68.5 ± 11.18 (284)</td>
<td>–0.19 (–1.99, 1.61)</td>
<td>0.836</td>
</tr>
<tr>
<td>Semester 2</td>
<td>71.4 ± 11.65 (282)</td>
<td>71.0 ± 11.85 (284)</td>
<td>0.28 (–1.47, 2.02)</td>
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<tr>
<td>English</td>
<td></td>
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</tr>
<tr>
<td>Semester 1</td>
<td>70.1 ± 11.03 (223)</td>
<td>69.8 ± 10.76 (223)</td>
<td>0.40 (–1.37, 2.17)</td>
<td>0.660</td>
</tr>
<tr>
<td>Semester 2</td>
<td>70.7 ± 10.69 (260)</td>
<td>70.6 ± 10.48 (262)</td>
<td>0.02 (–1.59, 1.62)</td>
<td>0.985</td>
</tr>
<tr>
<td>Science</td>
<td></td>
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</tr>
<tr>
<td>Semester 1</td>
<td>71.6 ± 10.43 (282)</td>
<td>71.7 ± 10.10 (284)</td>
<td>–0.06 (–1.62, 1.50)</td>
<td>0.938</td>
</tr>
<tr>
<td>Semester 2</td>
<td>73.4 ± 10.08 (282)</td>
<td>73.1 ± 10.34 (284)</td>
<td>0.23 (–1.27, 1.73)</td>
<td>0.759</td>
</tr>
</tbody>
</table>

\(^1\) All values are observed \(\bar{x}\) ± SD; \(n\) in parentheses. Tests of cognition were not carried out at baseline.

\(^2\) Estimate of intervention effect adjusted for design strata: age (mo), sex, and school (10 schools).

\(^3\) Visual recall measured on a scale ranging from 0 to 15.

\(^4\) Digits forward measured on a scale ranging from 0 to 16.

\(^5\) Digits backward measured on a scale ranging from 0 to 14.
power. However, whether such an improvement was due to improvements in the level and/or speed of the task performance is uncertain.

Information may have been transferred into working memory more rapidly in the fortified than in the unfortified group, possibly mediated by their improved iodine and zinc status (47–49). Improvements in cognitive performance have been reported in iodine-deficient schoolchildren supplemented with iodine (47, 50), although evidence for zinc is more limited (48). Improvements in cognitive function have also been observed among iron-supplemented children with iron deficiency anemia (21, 51, 52). However, because the iron status of the Thai children did not change (15), the visual recall improvement cannot be attributed to the iron fortificant.

In the Thai and South African studies (10), there was a positive intervention effect for the digit span forwards but not the digit span backwards test. However, in Thailand, this effect was not significant, perhaps because of the lower prevalence of iron and iodine deficiency (15) and the shorter study duration (10). Sensitivity of the digit span backwards subtest may be limited by a “floor” effect, the test being too difficult for most children because repeating digits in reverse order is not culturally familiar (43). Differences in the mode, dose, form, combination of micronutrients, and/or sample sizes also limits comparisons across studies.

Because of difficulties in interpreting the importance of changes in the cognitive function tests, we analyzed post hoc school grades for Thai, Mathematics, English, and Science. We did not observe any important improvement in academic achievement in accordance with 2 earlier reports of Thai schoolchildren supplemented with iron (3, 53). A short term improvement in learning, short-term memory, and attention span, based on the improvement in the visual recall test noted here, probably has little impact on educational deficits that result from prolonged micronutrient deficiencies, irrespective of whether the cognitive impairments caused by them have been corrected.

We believe that this RCT had many strengths. The groups were comparable at baseline and the study was double-blind, although the success of blinding was not assessed. Children were randomly assigned to the intervention group by an investigator (JEM) who was external to recruitment and had no information regarding potential prognostic factors. Finally, because of low attrition (15), the results can probably be generalized to children in northeast Thailand living in similar socioeconomic conditions. However, caution is needed when interpreting the results because of the number of outcomes and multiplicity of analyses.

In summary, a reduced prevalence of zinc and iodine deficiency and improved hemoglobin in northeast Thai schoolchildren consuming a seasoning powder fortified with zinc, vitamin A, iron, and iodine with a school lunch for 31 wk were associated with reductions in the incidence, but not in the duration, of respiratory-related illnesses and diarrhea and improved performance for the visual recall test. In contrast, there was no statistically significant intervention effect for anthropometric measures, digit span subtests, or academic achievement. The biological significance of such modest changes in morbidity rates and cognitive performance is uncertain. However, our RCT was only 31 wk in duration. A continued supply of these 4 micronutrients is probably necessary for persistent improvements in morbidity and cognitive function.

We thank all the schoolteachers and the children and their families who participated in this RCT and all the dedicated research assistants. Assistance with the statistical analyses of the morbidity data by Tor Strand, Center for International Health, University of Bergen, Norway, is gratefully acknowledged. The authors’ responsibilities were as follows—MSM: participated in the collection, analyses, and interpretation of the anthropometric, morbidity, and cognitive data with the assistance of TP, SG, and AG; JEM: performed the statistical analysis and interpreted the data; VC: developed the fortified seasoning powder and provided guidance on its use; TP (overall project field coordinator): participated in the data acquisition; BR: provided guidance on the assessment of cognition; PW, EW, JEM, and RSG: designed, implemented, and secured the funding for the study and assisted with the interpretation of the data; RSG, PW, and JEM: wrote the manuscript using a draft prepared by MSM. None of the authors had any financial or personal interest in any company or organization sponsoring the research.

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