

Can multi-micronutrient food fortification improve the micronutrient status, growth, health, and cognition of schoolchildren? A systematic review

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Micronutrient deficiencies compromise the health and development of many school-age children worldwide. Previous research suggests that micronutrient interventions might benefit the health and development of school-age children and that multiple micronutrients might be more effective than single micronutrients. Fortification of food is a practical way to provide extra micronutrients to children. Earlier reviews of (multiple) micronutrient interventions in school-age children did not distinguish between supplementation or fortification studies. The present review includes studies that tested the impact of multiple micronutrients provided via fortification on the micronutrient status, growth, health, and cognitive development of schoolchildren. Twelve eligible studies were identified. Eleven of them tested the effects of multiple micronutrients provided via fortified food compared to unfortified food. One study compared fortification with multiple micronutrients to fortification with iodine alone. Multi-micronutrient food fortification consistently improved micronutrient status and reduced anemia prevalence. Some studies reported positive effects on morbidity, growth, and cognitive outcomes, but the overall effects on these outcomes were equivocal.

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INTRODUCTION

Many school-age children around the world suffer from nutritional deficiencies, which can negatively affect their physical and mental development and increase susceptibility to infections.¹⁻⁵ It has been estimated that iron deficiency anemia (IDA) affects 53% of school-age children worldwide.⁶ Recent national studies from Thailand,⁷ the Philippines,⁸ Nicaragua,⁹ and Colombia¹⁰ observed average rates of national anemia prevalence ranging from 23% to 38%. Iodine deficiency has been observed with prevalence rates as high as 60–90% in schoolchildren from multiple African, Asian, and Eastern Mediterranean countries.¹¹⁻¹⁶ Micronutrient deficiencies are also

observed frequently in developed countries. According to the World Health Organization's (WHO) database on iodine deficiency, the prevalence of iodine deficiency among all the world's regions is actually highest in Europe.¹⁷ Iron deficiency is common among schoolchildren in Europe^{18,19} and the United States,²⁰⁻²⁴ especially in adolescent girls. Insufficient intakes of vitamin D and folate have also been observed among European children and adolescents.¹⁹

Multiple micronutrient (MMN) deficiencies often occur simultaneously as a result of a poor-quality diet. In developing countries, low dietary intakes of animal-source foods,²⁵ which are important sources of iron, zinc, vitamin A, B₁₂, and protein, can lead to MMN

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deficiencies.²⁶ Parasitic infections or diarrhea can also lead to MMN deficiencies due to limited absorption or utilization of nutrients.^{27,28} In wealthier countries, the overall quality of the diet of school-age children and adolescents is inadequate in large parts of the population. Families with a low socioeconomic status often cannot afford healthy diets²⁹; they have less access to micronutrient-rich foods like fruits, vegetables, meat, fish, and dairy.¹⁹ In addition, school-age children may develop a more independent eating pattern³⁰; this can include more out-of-home food consumption without supervision, which is likely to result in increased intake of foods of low nutritional value, such as soft drinks and salty snacks in place of micronutrient-rich foods.^{31,32}

At the same time, school-age children and adolescents are in a life stage of considerable physical and mental development. They experience growth spurts and sexual maturation, and girls begin menstruating³⁰; the brain continues to mature until young adulthood, and cognitive functions, in particular the higher-order cognitive functions (reasoning, planning, abstract thinking, etc.), develop and become more structured during this period.^{33–35} Meeting the nutritional demands required for this stage of development is crucial for optimal health, including physical and mental performance, and can influence health and productivity later in life. Excessively thin schoolchildren and adolescents can experience a delay in pubertal maturation and reduced muscular strength and work capacity, even reduced bone density later in life.¹ Undernutrition is also related to an increased risk of morbidity^{1,36}; vitamin A and zinc deficiency are associated with impaired immune function and higher susceptibility to infection and diarrhea.^{37,38} Mental development of children can be affected by malnutrition directly through insufficient supply of essential micronutrients, like iodine,¹⁷ leading to structural and functional impairment of the central nervous system.^{39,40} Micronutrient deficiencies can also have an indirect effect on mental and motor development. Undernourished or anemic children are less active and less likely to explore and interact with their environment, which can lead to suboptimal development.⁴¹

Interventions with (multiple) micronutrients have led to beneficial effects on linear growth,^{42,43} health,^{44–49} and cognitive development^{50–54} in schoolchildren. Most evidence is reported for iron, iodine, vitamin A, and zinc supplementation. There are data suggesting that combined supplementation of MMNs may have a greater effect on certain outcomes than supplementation with a single micronutrient. A meta-analysis on the effects of micronutrients on growth in children up to 18 years of age found that interventions with iron or vitamin A alone did not have an effect on either height or weight gain, whereas MMN interventions, 80% of which included

vitamin A, iron, and zinc, significantly improved linear growth and also had a small (not statistically significant) positive effect on weight gain.⁴²

Eilander et al.⁵⁵ reviewed the effects of MMNs delivered through either supplements or fortified foods on cognition in schoolchildren and found that MMNs had a small positive effect on fluid intelligence (reasoning ability) and academic performance. However, a subgroup analysis including only the studies that provided MMNs through fortified foods and excluding supplementation trials showed no beneficial effects.⁵⁵ The effect of the extra energy and nutrients provided through food that also benefited children in the control group may have made it difficult to detect an effect of the additional MMNs on the treatment group receiving fortified food.

It is evident that energy and protein have an impact on the growth, health, and development of children. Low energy and protein intakes are the primary cause for poor growth,⁵⁶ and undernutrition resulting from protein-energy deficiency is associated with increased susceptibility to infectious diseases.^{57,58} Fortification of food is a practical way to combine the benefits of energy repletion, adequate supply of fat and protein, and MMNs to optimize the growth and development of children. Previous reviews on the effect of MMN interventions and feeding programs in children exist,^{42,43,59–61} but they did not distinguish between MMNs provided in the form of a supplement or through fortified foods. A Cochrane systematic review by Kristjansson et al.⁶⁰ investigating the effectiveness of school feeding programs in low-income schoolchildren found that school meals and snacks can have a positive yet small impact on growth and cognitive outcomes. The review, based on 18 studies, deliberately excluded studies that modified the nutrient content of the school meals, including through fortification. A review performed by Rivera et al.⁶¹ distinguished particular interventions providing animal-source foods, but only one of the four studies described in the review included school-age children. A review conducted by Eilander et al.⁵⁵ investigated cognitive outcomes and included primarily MMN supplementation trials and a limited number of fortified food interventions. To our knowledge, the present review is the first that investigates the impact of MMN food fortification on the micronutrient status, growth, health, and cognitive development of school-age children.

LITERATURE SEARCH METHODS

A literature search for articles reporting the effects of MMN food fortification on the micronutrient status, growth, health, and cognitive development of schoolchildren was conducted using the PubMed, ISI Web of Knowledge, the Cochrane Database of Systematic Review

(CDSR), and the Central Register of Controlled Trials CENTRAL database. The search strategy was based on the Cochrane highly sensitive search strategy to identify reports of randomized controlled trials, which was expanded to incorporate other controlled experimental study designs, and subject-specific terms to identify eligible participant groups, interventions, and outcomes. Whenever possible, use was made of medical subject heading (MeSH) terms in PubMed, CDSR, and CENTRAL that related to children, micronutrients, fortified foods, and several of major health outcomes, such as growth, nutritional status, or cognition; the MeSH term “dietary supplements” was excluded in the search string. In ISI Web of Knowledge, the search string was adapted and consisted of relevant text words instead of MeSH terms. The search was restricted to articles published in the English language. Titles and abstracts from the initial search results were examined to identify potentially relevant studies; references of identified relevant studies and reviews were screened for further pertinent studies.

Eligibility criteria

Eligible study designs were restricted to experimental controlled efficacy or effectiveness studies including randomized controlled trials (RCT), quasi-experimental controlled clinical trials (CCT), and controlled before and after studies (CBA), as defined by the Cochrane Collaboration. Studies describing the mathematical method of randomization of individual subjects or clusters were classified as an RCT. Studies that used a non-mathematical method of randomization or that only mentioned a use of randomization but provided no description of the methodology were conservatively classified as a CCT. Studies that compared the intervention group to a comparable control before and after the intervention but did not use random allocation were classified as a CBA.

Eligible studies must have been conducted in school-age children. To qualify for inclusion, the vast majority of the study population had to be between 6 and 18 years of age; arbitrarily, the inclusion criteria was set at a minimum of 75% of the study sample being in this age range. Studies were excluded when the study population was specifically selected based upon health conditions that are rare in the general population, e.g., genetic disorders such as thalassemia or phenylketonuria. Children from developing countries who were selected because they suffered from undernutrition, anemia, parasitic infections, or HIV were not excluded as these conditions are not rare in most developing countries.

Eligible studies must have provided an MMN-fortified food intervention in at least one of the experimental conditions. MMN-fortified food was defined as

food to which a minimum of three micronutrients were added. Micronutrients from the B-vitamin complex were considered as one micronutrient, since these vitamins are frequently part of the same biological processes. Food interventions were defined as interventions providing fortified foods or beverages as well as fortificants that were added to foods or drinks on-site or at home. Studies were eligible if they properly tested the independent effect of MMN fortification by comparing an MMN-fortified food to either an unfortified food or a food fortified with only one or two micronutrients. Eligible studies assessed at least one of the following outcomes: biochemical measurements of micronutrient status or prevalence of micronutrient deficiencies; indicators of growth or body composition, prevalence of stunting, wasting, or underweight; indicators of morbidity (prevalence, incidence, duration, and/or severity), including absence from school; cognitive outcomes, including academic performance.

Evaluation of study results

Among the reported study outcomes, the following distinctions were made: 1) difference between groups in change from baseline to follow-up; 2) difference between groups at follow-up; or 3) difference within groups from baseline to follow-up. Differences between groups that took into account baseline values, either as covariates or by comparing change from baseline, were considered the most meaningful results. Differences were considered significant if the *P* value was less than 0.05.

The relevant information and results of the reviewed studies were assessed independently by two nutrition researchers (CB and NN). A research psychologist (CT) was consulted to gauge the validity and reliability of the methods used to assess cognitive outcomes.

SUMMARY OF FINDINGS

The literature search retrieved 1,053 citations. The vast majority of the citations were discarded because they were overview articles or reported on studies investigating the effects of a single micronutrient. Other major reasons for exclusion were that micronutrients were provided as supplements rather than through fortification of food, the intervention was provided to an inappropriate target population, or the study utilized a non-experimental design. The initial screening of titles and abstracts revealed 85 publications of potential relevance. After in-depth review and manual searching of reference lists, 12 eligible intervention studies were identified and included in the review. For an overview of the screening procedure see Figure 1.

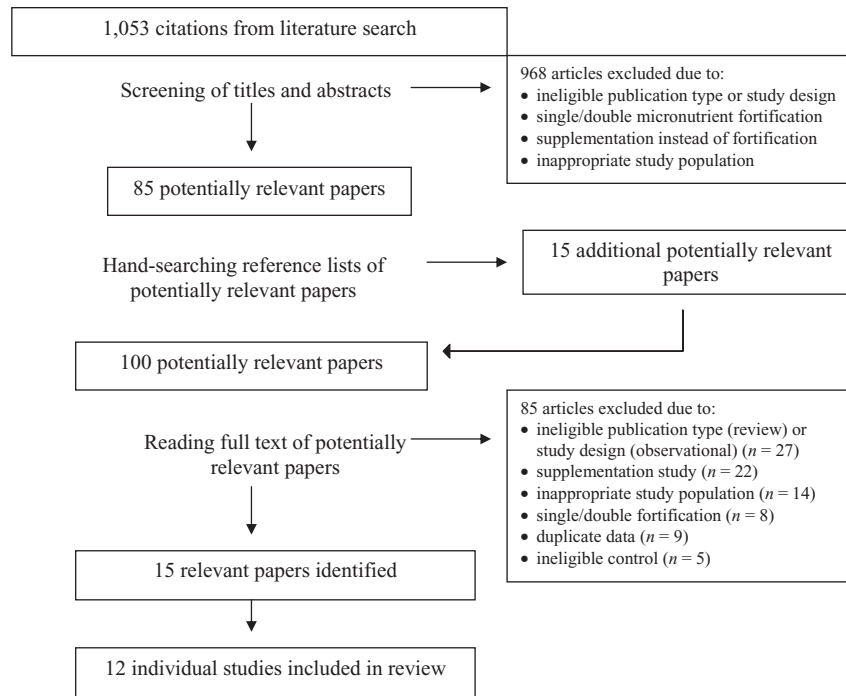


Figure 1 Flow chart of screening process for eligible articles.

Of the 12 eligible studies, 11 investigated the effect of MMN fortification by comparing the fortified food to an isocaloric unfortified food^{62–75}; one of these studies also included a third intervention arm in which no food intervention was provided,⁶² and one study compared the effect of MMN fortification to single fortification with iodine.⁷⁶ Eleven of the 12 studies were conducted in developing or transitional countries according to their Human Development Index 2009,⁷⁷ and 11 studies provided the intervention at school.^{62–76} The carriers used for fortification were beverages (6 studies),^{63,64,68,69,72} milk products (2 studies),^{62,65} biscuits (2 studies),^{67,71} or seasoning powder/salt (2 studies).^{74,76} In most studies the additional MMNs provided between 50 and 100% of the recommended dietary allowance⁷⁸ of the individual micronutrients daily. All foods were fortified with a combination of at least iron and vitamin A or β -carotene. Iodine, zinc, B-vitamins and vitamin C were usually included. Three studies also provided eicosapentaenoic acid, docosahexaenoic acid, taurine, or inulin together with the MMN intervention while these ingredients were not provided to the control group.^{62,63} For an overview of the individual study characteristics, see Table 1. Since 11 of the 12 studies compared an MMN-fortified food to an unfortified food, the results from these studies are focused upon. The results of the remaining study comparing MMN-fortified salt to iodized salt, which only investigated effects on micronutrient status, will be summarized briefly. Table 2 gives a concise overview of all outcomes

evaluated by the studies reviewed, while Table 3 provides a summary of each study's findings and limitations.

Effects on micronutrient status

Ten studies assessed the effect of MMN fortification of foods compared to unfortified foods on the micronutrient status or prevalence of deficiencies in children (Table 3). All 10 studies measured a statistically significantly greater improvement in micronutrient status in the intervention group compared to the control group, taking baseline values into account. The most frequently observed (and investigated) effects were increases in hemoglobin (Hb), iron, vitamin A, iodine, and folate status. All 10 studies assessed Hb status; seven studies reported a significant beneficial effect of MMN fortification on Hb status or anemia prevalence, taking baseline values into account. In addition, one study reported a significantly lower prevalence of anemia at follow-up in the MMN group (14.9%) compared to the control group (28.8%) ($P = 0.03$), while anemia prevalence at baseline was comparable.⁶⁴ Two studies reported a significant effect in a sub-sample of children who were initially anemic⁶⁵ or a significant inverse relationship between initial Hb levels and response to the MMN intervention.⁶⁴ Only one study, which was conducted in well-nourished Australian children who had adequate Hb levels at baseline, did not find any effect on Hb or anemia prevalence.⁶³

Table 1 Characteristics of the studies assessing effects of MMN-fortified foods on health outcomes in school-age children.

Reference	Study design	Age of subjects	No. of subjects	Sample characteristics	Study location	Intervention product and administration	Energy (and macro-nutrient) content per daily serving	Duration of intervention	MMN fortification (daily dosage)	Retention rate	Compliance	Outcomes assessed	Notes
MMN-fortified food versus unfortified food interventions													
Abrams et al. (2003) ⁶⁸	CBA	6–11 y	311	Urban, low SES	Gaborone, Botswana	240 mL fruit-flavored beverage, daily	100 kcal	8 weeks	7.0 mg iron, 2.4 mg β -carotene, 60 μ g iodine, 3.75 mg zinc, 0.4 mg B ₂ , 2.7 mg niacin, 0.5 mg pyridoxine, 140 μ g folic acid, 1.0 μ g B ₁₂ , 60 mg vitamin C, 7.5 mg vitamin E, 120 mg tricalcium phosphate	85%	89%	Iron, zinc, vitamin A, B ₂ , folate, B ₁₂ and Hb status, anemia prevalence, height, weight, MUAC	At baseline 12% of children anemic in combination with a second micronutrient deficiency. Less than 10% were stunted or wasted. Children with severe anemia (Hb < 60 g/L), excessive thinness (<15 kg), and acute or chronic illness were excluded
Ash et al. (2003) ⁷²	CCT	6–11 y	830	Rural	Mpwapwa district, Maasai Steppe, Tanzania	250 mL fruit-flavored beverage, 5 days/week	90 kcal	6 months	5.4 mg iron, 525 μ g RE vitamin A, 45 μ g iodine, 5.25 mg zinc, 72 mg vitamin C, 0.6 mg vitamin B ₂ , 0.7 mg vitamin B ₆ , 141 μ g folic acid, 3.0 μ g vitamin B ₁₂ , 10.5 mg vitamin E	93%	80%	Iron, vitamin A status and deficiency, Hb status, anemia prevalence, height, weight	Study in malaria endemic region; at baseline 20% vitamin A deficient, ~20% anemic; children with severe anemia (Hb < 70 g/L), xerophthalmia, or serious chronic disease were excluded. Children with intestinal helminth infections at baseline received medication
Hyder et al. (2007) ⁶⁹	RCT	Mean age 12.0 y	1125	Girls, rural, low SES	Sherpur district, Bangladesh	200 mL of fruit-flavored beverage, 6 days/week on school days	Not reported	12 months	7.0 mg iron, 388 μ g RE vitamin A, 75 μ g iodine; 7.5 mg zinc, 120 mg vitamin C, 0.91 mg B ₂ , 5.0 mg niacin, 1.0 mg B ₆ , 120 μ g folic acid, 1.0 μ g B ₁₂ , 10 mg vitamin E	92%	Not reported	Iron, zinc, and vitamin A status and deficiency, Hb status, anemia prevalence, height, weight, MUAC, inflammation (C-reactive protein)	At baseline high prevalence of zinc (58%) and iron (31%) deficiency. 80% were excessively thin (BMI < 16 kg/m ²) at baseline. Children with severe anemia (Hb < 70 g/L), gitter, night blindness, or acute infection were excluded
Lien do et al. (2009) ⁶²	CCT	7–8 y	454	Not specified	Yen Phong District, Bac Ninh Province, Northern Vietnam	250 mL milk, twice daily, 6 days/week	380 kcal (15.5 g protein)	6 months	6.3 mg iron, 4.5 μ g RE vitamin A; 22 μ g iodine; 3.5 mg zinc, 162 mg vitamin C, 0.45 mg vitamin B ₁ ; 35 mg vitamin B ₂ ; 12.2 mg vitamin E; 2.9 IU vitamin D; 225 mg Ca, 15 mg magnesium, 1.3 mg manganese; 60 mg potassium, 5 g inulin vitamin K, B ₃ , B ₆ , folate, pantothen, biotin, selenium, taurine, in unspecified amounts	Not reported	Not reported	Stool bacteria load, accuracy, efficiency of working, short-term memory, IQ, mathematics, Thai language	Study sample with poor overall nutritional status; 30–50% prevalence of anemia, zinc deficiency, stunting and underweight at baseline. Intervention with MMN-fortified milk versus unfortified regular milk versus no food. MMN-fortification included inulin and taurine.
Manger et al. (2008) ⁷⁴ Winichagoon et al. (2006) ⁶⁶	RCT	5.5–13.4 y	569	Rural, low SES	Trakan Phutphon district, Northeast Thailand	Seasoning powder added to daily lunch (generally containing 1.5 mg iron, 1.3 mg zinc, and 26 μ g RE vitamin A), 5 days/week	288 kcal (9.9 g protein)	31 weeks	5.0 mg iron, 270 μ g RE vitamin A, 50 μ g iodine, 5.0 mg zinc	98%	75%	Iron, iodine, zinc, and vitamin A deficiency, Hb status, height, weight, MUAC, skinfold thickness, height-for-age, weight-for-age, weight-for-height	At baseline, high prevalence of anemia (~30%), zinc deficiency (~54%) and iodine deficiency (~70%); one-third of children had parasitic infections. Children with severe anemia (Hb < 80 g/L) or acute or chronic illness were excluded

Nga et al. (2009) ⁶⁷	RCT, 2 × 2 design	6–8 y	510	Rural, low SES	Hung Yen Province, Vietnam	30 g biscuits, 5 days/week	133 kcal	4 months	6.0 mg iron, 300 µg RE vitamin A, 35 µg iodine, 5.6 mg zinc, 1.0 mg B ₁ , 0.9 mg B ₂ , 1.1 mg B ₆ , 10.5 mg niacin, 120 µg folic acid, 1.5 µg B ₁₂ , 18 µg biotin, 28.4 mg vitamin C, 150 mg Ca, 74 µg vitamin D, 40 mg Mg, 6.8 µg Se, 37.8 mg K, 70 mg Ph, 3 mg pantothenic acid, 2.8 µg vitamin E, 10 µg 5 vitamin K	91%	95%	Iron, iodine, and vitamin A status and deficiency, anemia prevalence, parasite infection	Study sample with overall poor nutritional status: 25% anemic, 55% zinc deficient, 44% iodine deficient; 82% parasitic infection, 29% underweight. Children with Hb < 80 g/L, severe malnutrition (WHZ < 3SD, > 2SD, or BMI > 25) or chronic illness were excluded. 2 × 2 design: IMMN fortification and deworming treatment
Osendarp et al. (2007) ⁶³	RCT, 2 × 2 design	6–10 y	396	Urban, high SES	Adelaide, Australia	100 mL fruit-flavored soy drink, consumed at home, daily	130 kcal (8.6 g protein)	12 months	10 mg iron, 400 µg RE vitamin A, 5.0 mg zinc, 150 µg folate, 1.0 mg B ₆ , 1.5 µg B ₁₂ , 45 mg vitamin C	70%	76%	Iron, zinc, folate, vitamin B ₁₂ , DHA, EPA, and Hb status, general intelligence, verbal learning and memory, visual attention, academic performance	Study sample with good overall nutritional status: less than 5% with micronutrient deficiencies; 1% anemic. Severely malnourished (WHZ < -3SD) or anemic (Hb < 80 g/L) children were excluded. 2 × 2 design: MMN fortification, omega-3 fatty acid fortification
Osendarp et al. (2007) ⁶³	RCT, 2 × 2 design	6–10 y	384	Urban, low SES, marginally nourished	Jakarta, Indonesia	100 mL fruit-flavored soy drink and three biscuits, 6 days/week	230 kcal (12.6 g protein)	12 months	11 mg iron, 400 µg RE vitamin A, 5.0 mg zinc, 45 mg vitamin C, 1.0 mg B ₆ , 150 µg folate, 1.5 µg B ₁₂	96%	86%	Iron, zinc, folate, vitamin B ₁₂ , DHA, EPA, and Hb status, general intelligence, verbal learning and memory, visual attention, academic performance	At baseline ~20% of children were iron or zinc deficient, 10% anemic. Severely malnourished (WHZ < -3SD), anemic (Hb < 80 g/L), or well-nourished (WHZ > 0.44) children were excluded; 2 × 2 design: MMN fortification, omega-3 fatty acid fortification
Sivakumar et al. (2006) ⁶⁵ Sarma et al. (2006) ⁷⁰ Shatrugna et al. (2006) ⁷³ Vazir et al. (2006) ⁷⁵	CCT	6–18 y	328	Middle SES	Near to Hyderabad, India	150 mL milk porridge	320 kcal (14.8 g protein)	14 months	14 mg iron, 400 µg RE vitamin A, 75 µg iodine, 2.3 mg Zn, 80 mg vitamin C, 0.7 mg vitamin B ₁ , 1.6 mg vitamin B ₂ , 0.9 mg niacin, 2.0 mg vitamin B ₆ , 200 µg folic acid, 1.0 µg vitamin B ₁₂ , 2.5 µg vitamin D, 224 mg Ca	74%	Not reported	Iron, iodine, zinc, calcium, vitamin A, B ₁ , B ₂ , B ₆ , folate, B ₁₂ , C, D, and Hb status, parathyroid hormone, triiodothyronine, thyroid-stimulating hormone, prevalence of goiter, Bitot's spots, angular stomatitis, glossitis cheilosis, bleeding gums, height, weight, height-for-age, weight-for-age, skinfold thickness, body composition, bone mineral content and density, intelligence, memory, attention and concentration, scholastic achievement	Study sample with overall poor nutritional status: 55% anemic, high prevalence of folate (100%), other B vitamins (65%), and vitamin A and C (55%) deficiency. All children received deworming treatment twice at 6-month intervals.

Table 1 Continued

Reference	Study design	Age of subjects	No. of subjects	Sample characteristics	Study location	Intervention product and administration	Energy (and macro-nutrient) content per daily serving	Duration of intervention	MMN fortification (daily dosage)	Retention rate	Compliance	Outcomes assessed	Notes
Solon et al. (2003) ⁶⁴	CCT, 2 × 2 design	Mean age, 10 ± 2.1 y	851	Rural	Balete, Batangas, Philippines	200 mL beverages, twice daily, on school days	Not reported	16 weeks	9.6 mg iron, 240 µg RE vitamin A, 96 µg iodine, 7.5 mg zinc, 150 mg vitamin C, 0.92 mg vitamin B ₂ , 5.0 mg niacin, 1.0 mg vitamin B ₆ , 120 µg folic acid, 1.0 µg vitamin B ₁₂ , 5.0 mg vitamin E	95%	Not reported	Iodine status, weight, height, height-for-age, weight-for-age, weight-for-height, anemia prevalence, physical fitness, heart rate, verbal, nonverbal, and quantitative mental abilities	Study sample with overall poor nutritional status: 52% anemic, 90% iodine deficient, 54% with helminth infections. Overall prevalence of moderate-to-severe malnutrition in study area was 25%. Children with Hb < 80 g/L were excluded. 2 × 2 design: MMN fortification and deworming treatment
Van Stuijvenberg et al. (1999) ⁷¹	CCT	6–11 y	228	Rural, low SES	60 km NW of Durban, KwaZulu-Natal, South Africa	3 shortbread biscuits and 150 mL cold drink, 5 days/week	250 kcal (4.1 g protein)	12 months	5.0 mg iron, 2.1 mg β-carotene, 120 µg iodine, 90 mg vitamin C	Not reported	93%	Iron, iodine, and vitamin A status and deficiency. Hb status, anemia, and goiter prevalence, height, weight, height-for-age, weight-for-age, white blood cell counts, illness-related absence, processing speed, working memory	At baseline 41% of children were vitamin A deficient, 20% had goiter and 28% had anemia. One-third of children had parasite infections. All children were dewormed at baseline and during 4-month intervals. A school-feeding program had been in place for 2 years before baseline assessments but was stopped before study started; Salt iodization became mandatory halfway through study → usual consumption switched from non-iodized to iodized salt
MMN-fortified versus single-nutrient-fortified food Zimmermann et al. (2004) ⁷⁶	CCT	6–14 y	159	Rural	Rif mountain village, northern Morocco	2 kg of salt delivered to households each month (~10 g salt per day per child)	Not reported	10 months	2.0 mg iron, 60 µg RE vitamin A, and 25 µg iodine per g of salt versus iodized salt only (2.5 µg per g). Daily intake ~19 mg iron, 570 µg vitamin A, 240 µg iodine	99%	100%	Iron, iodine, vitamin A status and deficiency, prevalence of iron deficiency anemia	Effectiveness study. MMN-fortified salt versus iodized salt. Study carried out in area endemic for goiter

Abbreviations: BMI, body mass index; CBA, controlled before and after study (observations are made before and after the intervention, both in a group that receives the intervention and in a group that does not); CCT, controlled clinical trial (controlled trial where treatment allocation is performed with intent to prevent bias using some non-mathematical method such as a coin flip, days of the week, or even-odd numbers); Hb, hemoglobin; IQ, intelligence quotient; MMN, multiple-micronutrient; MUAC, middle-upper-arm circumference; RBC, red blood cell; RCT, randomized controlled trial (controlled clinical trial in which treatment allocation is randomized using some mathematical method such as a random-numbers table); SES, socioeconomic status; WHZ, weight-for-height z-score.

Table 2 Summary of results of intervention studies testing the effects of MMN–fortified food on health and developmental outcomes.

Reference	Micronutrient deficiencies				Growth and weight			Morbidity				Cognitive performance			
	Iron	Hb/Anemia	Iodine	Vitamin A	Zinc	B–vitamins	Height/stunting	Weight/BMI/underweight	Respiratory–related diseases	Diarrhea	Other diseases (markers)	Memory	Fluid intelligence	School performance	Other cognitive outcomes
MMN–fortified food versus unfortified food															
Abrams et al. (2003) ⁶⁶	✓	✓	–	×	–	✓	×	✓	–	–	–	–	–	–	–
Ash et al. (2003) ⁷²	✓	✓	–	✓	–	–	✓	✓	–	–	–	–	–	–	–
Hyder et al. (2007) ⁶⁹	✓	✓	–	✓	×	–	×	–	–	×	–	–	–	–	–
Lien do et al. (2009) ⁶²	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Manger et al. (2008) ^{66,74}	×	–	–	×	–	–	×	×	–	–	–	–	–	–	–
Nga et al. (2009) ⁶⁷	✓	✓	✓	✓	✓	–	–	–	–	–	–	–	–	–	–
Osendarp et al. (2007) ⁶³ (Australia)	✓	×	–	–	×	✓	–	–	–	–	–	–	–	–	–
Osendarp et al. (2007) ⁶³ (Indonesia)	✓	✓	–	–	×	✓	–	–	–	–	–	–	–	–	–
Sivakumar et al. (2006) ^{65,70,73,75}	✓	(✓) ¹	✓	✓	×	✓	✓	✓	×	×	✓ ⁶	×	×	×	×
Solon et al. (2003) ⁶⁴	–	✓	✓	–	–	–	×	×	–	–	(✓) ⁷	–	–	–	(✓) ¹²
van Stuijvenberg et al. (1999) ⁷¹	✓	✓	✓	✓	–	–	×	×	×	✓	–	–	–	–	×
MMN–fortified food versus single–fortified food															
Zimmerman et al. (2004) ⁷⁶	✓	✓	–	–	–	–	–	–	–	–	–	–	–	–	–

¹ Effect only in deficient/anemic/malnourished children.

² Outcome measure: prevalence of inflammation.

³ Outcome measure: stool bacteria load.

⁴ Outcome measure: fever.

⁵ Positive interaction effect with deworming treatment on parasitic infection, no independent effect of MMN.

⁶ Outcome measure: duration of all reported diseases.

⁷ Significant effect on heart rate only in anemic or iodine-deficient subsample.

⁸ Effect on verbal learning and memory, only in girls.

⁹ Results on academic performance were integrated in a cluster of other cognitive tests.

¹⁰ Outcome measure: accuracy and efficiency of working.

¹¹ Outcome measure: attention and concentration.

¹² Total cognitive score; effect only in severely to moderately anemic children.

¹³ Outcome measure: speed performance.

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✓

✓ Significant beneficial effect of MMN (comparing change from baseline between or within groups, or means between groups at follow-up).

– Parameter not assessed.

Abbreviations: BMI, body mass index; Hb, hemoglobin.

Table 3 Overview of the results of studies assessing effects of MMNs provided in a food matrix on the biochemical indicators of nutritional status, anthropometry, morbidity, and cognitive outcomes in school-age children.

Reference	Statistical analyses	Nutritional status results	Anthropometric results	Morbidity results	Cognitive results	Notes
Abrams et al. (2003) ⁸⁸	MMN-fortified food versus unfortified food intervention Differences in change from baseline to follow-up between groups were tested using ANCOVA, adjusted for age, sex, weight, and group. For between-group differences in prevalence of deficiencies/anemia at follow-up, odds ratios were computed using logistic regression, controlling for age, sex, and weight.	Significant beneficial effect of MMN on change in serum ferritin, folate, riboflavin, Hb, and MCV versus control ($P < 0.05$); no effects on vitamin B ₁₂ and retinol status. The odds of zinc (OR = 0.29), folate (OR = 0.02), vitamin B ₉ (OR = 0.36) deficiency, and anemia (OR = 0.48) at follow-up were significantly lower in the MMN versus control group ($P < 0.05$). Hb levels decreased and prevalence of anemia increased in both groups (but much more in the control group).	Significant beneficial effect of MMN on change in weight, BMI, MUAC, and weight-for-age Z-score versus control ($P < 0.01$), but no effect on height.	None	None	Children in the MMN group were 5.4 months older than children in the control group. Analyses were adjusted accordingly. Baseline data of zinc status not available. Different measurement methods used for measuring Hb at baseline and follow-up. Iron was provided in chelated form.
Ash et al. (2003) ⁷²	Differences in change from baseline to follow-up between groups were tested using independent <i>t</i> -test. Differences in change from baseline to follow-up within groups were tested using paired <i>t</i> -tests.	Significant beneficial effect of MMN on change in serum ferritin, protoporphyrin, Hb levels, and anemia prevalence versus control ($P < 0.01$). Hb levels decreased and prevalence of anemia increased in both groups (but much more in the control group). Prevalence of vitamin A deficiency decreased significantly in MMN group (from 21% to 11%, <i>P</i> -value not given) but not in control group.	Significant beneficial effect of MMN on change in weight, height, and BMI versus control ($P = 0.001$). Children in MMN group gained on average 0.55 kg more weight, 0.57 cm more height, and 0.35 kg/m ² BMI compared to control group.	None	None	Study sample with poor overall nutritional status. Higher prevalence of iron deficiency at baseline in MMN (13%) than control group (5%). No adjustments of analyses for demographic or baseline values. Baseline data were assessed in dry season (plenty of food, little malaria) whereas follow-up fell in wet season (little food, plenty of malaria) which might have affected nutritional status.
Hyder et al. (2007) ⁶⁹	Differences in change of biochemical indicators of nutritional status from baseline to follow-up between groups were tested using independent <i>t</i> -test. Differences in changes of anthropometric measures from baseline to follow-up between groups were tested using general linear modeling adjusted for baseline values. Comparisons between proportions were tested using Wilcoxon's Signed Rank test. Differences in means within groups were tested using paired <i>t</i> -tests. For differences in prevalence of deficiencies at follow-up between groups, odds ratios were computed using logistic regression adjusted for age. Change in anemia prevalence from baseline to follow-up within groups tested by McNamara's test.	Significant beneficial effect of MMN on change in serum ferritin, retinol, and Hb levels ($P < 0.001$) but not zinc versus control after 6 months. Significant beneficial effect of MMN on change in prevalence of ID and VAD versus control ($P < 0.01$) after 6 months. Prevalence of IDA decreased significantly in MMN ($P < 0.01$) but not control group. At 6 months, girls in control group were significantly more likely to have VAD (OR = 5.47), ID (OR = 5.38), IDA (OR = 11.19), or anemia (OR = 2.04) ($P < 0.05$) compared to MMN group. Anemia prevalence decreased within MMN group during first 6 months ($P < 0.001$) and increased within the control group until the end of the study ($P = 0.02$). No further effects on nutritional status were seen between 6 and 12 months except for further increasing serum ferritin levels.	Significant beneficial effect of MMN fortification on change in weight, MUAC, and BMI versus control ($P < 0.001$) at 6 months. No further effects were seen between 6 and 12 months. No significant effects were seen on increment in height between groups.	Prevalence of inflammation (high CRP) did not differ between groups throughout the study.	None	Overall good quality of study. Groups similar at baseline. No adjustment of analyses for demographic values. Study sample with poor overall nutritional status.

Lien do et al. (2009) ⁶²	Differences in change of morbidity outcomes from baseline to follow-up between the three groups (MMN-fortified/unfortified/ no food intervention) were tested using ANOVA. Differences in the final cognitive scores between the three groups were tested using ANCOVA.	None	Significant: beneficial effect of MMN-fortified milk versus unfortified milk on change in total bacteria, bifidobacteria, and bacteroides at 3 months ($P < 0.05$), with higher amounts of bacteria in the MMN group.	Measurements: exercises to determine the speed, accuracy, and efficiency of working by making use of Bourdon alphabets; exercises in memorizing words and numbers (no references). No significant difference between MMN-fortified and unfortified group at follow-up: the fortified milk group performed better than milk group on recall of words and digits but difference did not reach significance (author's personal communication).	Higher total bacteria load at baseline in MMN than unfortified group. No adjustments of analyses for demographic and baseline values. MMN-fortified food also included inulin and taurine. Study sample with poor overall nutritional status. Qualified cognitive test assessors and culturally relevant tests adapted from the WISC tests (author's personal communication), thus optimizing tests' psychometric properties.
Manger et al. (2008) ⁷⁴ and Winichagoon et al. (2006) ⁶⁶	Differences in means between groups at follow-up were tested using multiple linear regression analysis (MANOVA) adjusted for age, sex, school, and baseline value (not available for cognitive tests). For differences in prevalence of deficiencies between groups at follow-up, odds ratios were computed using logistic regression adjusted for age, sex, and school. Change in anemia prevalence from baseline to follow-up between groups was tested using ratio of risk ratios. Differences between groups in incidence of morbidity episodes at follow-up were expressed as rate ratios using negative binomial regression, adjusted for age, sex, and schools.	No significant differences in any of the anthropometric measures (height, weight, knee height, BMI, skinfold thickness, MUAC) at follow-up between MMN and control groups.	At follow-up MMN group had significantly lower incidence of respiratory-related symptoms (RR = 0.83) and diarrhea (RR = 0.38) versus control ($P < 0.05$). No differences between incidence of fever, skin rash, or other diarrheal-related diseases between groups at follow-up. No significant differences at follow-up in duration of morbidity episodes (i.e., respiratory-related diseases, runny nose, or cough) between groups.	Measurements: digit span forward, digit span backward (from WISC-III), and visual recall task with familiar object; both tests under condition of increased anxiety induced by instruction effects. Average grade scores. Significantly higher scores of MMN versus control group at follow-up on visual recall.	Overall good quality of the study. Groups similar at baseline. Study sample with poor overall nutritional status. Both groups experienced improvements in biochemical parameters, which may have been affected by the improved school meals given to both groups. Iron provided as H-reduced elemental iron, with low bioavailability. Vitamin A provided as retinyl palmitate, which is instable in dry matrices. Cognitive assessment does not follow standard procedure: The observed changes could be due to the impact of micronutrients on memory or on reduction of anxiety in all or in a subgroup of anxiety-prone children.
Nga et al. (2009) ⁶⁷	Differences in means between groups at follow-up were tested using ANCOVA adjusted for baseline values, sex, age, and CRP (nonparametric test used if data not normally distributed); multiple comparisons made with Bonferroni post hoc test. For differences in prevalence of deficiencies and infections between groups at follow-up, odds ratios were computed using logistic regression adjusted for baseline values, age, sex, and CRP.	None	No significant effect of MMN fortification alone on parasitic infections at follow-up, but significant interaction with deworming treatment: a greater reduction in prevalence of parasitic infection observed in children who received MMN plus deworming treatment compared to only deworming treatment ($P < 0.02$).	None	Overall good quality of the study. Groups similar at baseline. Study sample with poor overall nutritional status.

Table 3 Continued

Reference	Statistical analyses	Nutritional status results	Anthropometric results	Morbidity results	Cognitive results	Notes
Osendarp et al. (2007) ⁶³ Australia	Differences in change from baseline to follow-up between groups were tested using ANCOVA adjusted for baseline values, sex, age, and cohort of recruitment.	Significant beneficial effect of MMN on change in serum ferritin, body iron stores, RBC folate, and vitamin B ₁₂ versus control ($P < 0.05$); but no effect on serum zinc or Hb levels.	None	None	Measurements: digits backwards, coding, block design, and vocabulary (4 sub-scales from WISC-III), visual attention 2, fluency (2 sub-scales from NEPSY). Academic tests were reading, spelling, and mathematical reasoning (3 tests from WIAT Screener). After factorial analysis of the cognitive tests, tests were clustered into factor 1 (fluid intelligence), factor 2 (verbal learning and memory), and factor 3 (attention and concentration). Significant beneficial effect on change in factor 2 in MMN versus control group.	Two recruitment rounds were necessary; baseline values of children from the different rounds were different, adjusted accordingly. Study sample with good overall nutritional status. Only small sub-sample (26% of total sample) available for biochemical parameters because parents and children refused blood sampling. High number of participants (30%) was lost to follow up. Standardized cognitive tests of high psychometric value, psychometric value, qualified assessors.
Osendarp et al. (2007) ⁶³ Indonesia	Differences in change from baseline to follow-up between groups were tested using ANCOVA, adjusted for baseline values, sex, and age.	Significant beneficial effect of MMN on change in serum ferritin, transferrin receptor, body iron stores, Hb levels, RBC folate, vitamin B ₁₂ , plasma DHA, and total plasma omega-3 versus control ($P < 0.05$, but no effect on serum zinc).	None	None	Measurements: same as in Australia (Osendarp 2007 ⁶³), except reading test in Bahasa language (Neale Analysis of Reading) and no spelling test. No significant effects in MMN versus control group on change in cognitive scores based on omnibus ANOVA. A posteriori analyses showed significant beneficial effect of MMN on change in factor 2 (verbal learning and memory) versus control in girls but not boys.	Overall good quality of the study. Study sample with poor nutritional status. Standardized cognitive tests of high psychometric value, qualified assessors. Verbal memory test had floor effects that question its validity in this sample; could explain lack of replication of results from Australian sample.
Sarma et al. (2006) ⁷⁰ Sivakumar et al. (2006) ⁶⁵ Shatrugna et al. (2006) ⁷³ Vazir et al. (2006) ⁷⁵	Differences in means between groups and change from baseline to follow-up between groups up were tested using weighted paired <i>t</i> -tests. If baseline means differed between groups, these differences were corrected using a regression model. Differences in proportions between groups were tested using the Wilcoxon signed rank test.	Significant beneficial effect of MMN fortification on change of RBC folate, B ₂ status as well as on thyroid-stimulating hormone (TSH) and parathyroid hormone (PTH) versus control ($P < 0.001$). No significant effect of MMNs on change of vitamin B ₁ , B ₆ , B ₁₂ , vitamin C, zinc, calcium, phosphorus, and Hb levels. Amongst sub-sample of anemic children, mean Hb levels at follow-up were significantly higher compared to control ($P < 0.05$). At follow-up, vitamin C and ferritin levels were significantly higher in MMN compared to control group ($P < 0.001$). No significant differences observed between MMN and control groups on prevalence of clinical signs of deficiency throughout study, i.e., goiter, Bitot's spots, angular stomatitis, glossitis cheilosis, bleeding gums.	Significant beneficial effect of MMN fortification on change in weight, height, BMI, HAZ, WAZ, and weight velocity versus control ($P < 0.05$). Also, significant beneficial effect of MMN fortification on change in fat-free mass, percentage of fat, whole-body bone mineral content, whole-body area and neck mineral density versus control ($P < 0.05$), but no effect on bone parameters of hip or spine.	No significant effect of MMN fortification on number of episodes of illness (i.e., fever, cough and cold, diarrhea, ear infection), but mean duration of all diseases was significantly shorter in MMN group (5 days) compared to control (7.4 days) ($P < 0.05$).	Measurements: Malin's intelligence scale for Indian children (Indian adaptation of WISC-R) including 6 verbal and 5 performance sub-scales; standardized scores of verbal IQ, performance IQ, and general IQ, PGI memory scale (7 sub-scales plus total score), Knox-cube imitation test, letter cancellation test, 3 academic scores (math, science, social studies), and the aggregated score. Significant beneficial effect of MMN on change in Knox-cube test. Significantly lower scores on letter cancellation tests (attention and speed) in MMN versus control group at follow up, but no significant effect on change in scores from baseline to follow-up.	Two classes in each grade were randomized to MMN or control treatment and considered a matched pair. Paired <i>t</i> -tests were applied to these matched pairs to test for differences. Study sample with poor overall nutritional status. Groups similar at baseline. No adjustments of analyses for demographic variables. Biochemical assessment only in subsample ($n = 327$). High number of participants (25%) lost to follow up. Data on sickness based on self-reporting. Cognitive assessment methods ensure good psychometric properties: selected tests standardized and validated for this population; tests piloted; assessors trained. Statistical methods lack consistency. Inconsistencies in outcomes as reported and presented in figures.

Solon et al. (2003) ⁶⁴	Differences in means between groups and change from baseline to follow-up between groups were tested using ANOVA. If significant, a multiple-range test was done to identify which groups differed from each other.	Significant beneficial effect of MMN fortification on change in UI versus control ($P < 0.001$) but not Hb levels. Significant inverse correlation between baseline UI status and increase in UI levels upon fortification, $P < 0.0001$. Effect of MMN fortification on change in iodine status was significantly higher in non-anemic children than in anemic children ($P < 0.01$). Significant inverse correlation observed between baseline Hb levels and effect of MMN fortification on Hb levels ($P < 0.0001$). The number of children who remained anemic at follow-up was significantly lower in MMN (15%) versus control group (29%) ($P = 0.03$).	No significant effect of MMN fortification on any anthropometric outcomes versus control (height, weight, weight-for-age, height-for-age, and weight-for-height).	No significant effect but positive trend seen for MMN fortification on change in heart rate and fitness index. Significant effects on change in heart rate were observed in sub-sample of anemic and iodine-deficient children ($P < 0.05$).	Measurements: Primary mental abilities test for Filipino children (not published). No effects of MMN versus control based on omnibus ANOVA. A posteriori analyses on small sub-sample of moderately to severely anemic children ($n = 24$) show a significant beneficial effect of MMN on total cognitive score versus control.	Groups similar at baseline. No adjustments of analyses for demographic or baseline values. Study sample with poor overall nutritional status. Psychometric properties of cognitive test unknown and test administration differs between grades; this jeopardizes the chances of detecting effects.
van Stuijvenberg et al. (1999) ⁷¹	Differences in change from baseline to follow-up between groups were tested using Wilcoxon 2-sample test. Differences in prevalences of deficiencies between groups were tested using repeated-measures ANOVA for categorical data. Differences in absent days between groups were tested using the chi-square test.	Significant beneficial effect of MMN fortification on change in all markers of iron status, UI, serum retinol, Hb levels, and Htc versus control ($P < 0.0001$). Prevalence of vitamin A, iron, and iodine deficiency decreased significantly more in MMN group versus control ($P < 0.0001$), but no effect of MMN fortification was observed on prevalence of goiter or anemia.	No significant effect of MMN fortification on any anthropometric outcomes versus control (height, weight, weight-for-age, height-for-age).	Significantly fewer absent days due to diarrhea-related illness in MMN group versus control (52 versus 79 days, $P = 0.013$); fewer days were missed due to respiratory illness in MMN versus control group.	Measurements: Five tests recording speed performance – digit copying, counting letters, cancelling letters, reading numbers, counting backward. Performance under time constraint: verbal fluency, writing crosses, digit span forward, digit span backward. Outcomes: significant beneficial effect of MMN on digit span show greater and more treatment effects of MMN in children with low serum ferritin and Hb and those with goiter at baseline.	No adjustments of analyses for demographic values. Nothing mentioned on double-blinding and dropout rate. Methods used for cognitive assessment follow published guidelines for nutrition studies; tests selected for their good psychometric properties; cultural adaptation, piloting, standardized procedure (trained assessors) optimizing tests psychometric properties. Study sample with poor nutritional status. Salt iodization became mandatory halfway through study and usual consumption switched from non-iodized to iodized salt.
MMN-fortified food versus single-fortified food intervention Zimmermann et al. (2004) ⁶⁶	Differences in change from baseline to follow-up between groups were tested using two-factor repeated measures ANOVA. If significant, independent t-tests and paired t-tests were used to test for differences between and within groups. Differences in change of prevalence of deficiencies from baseline to follow-up between groups were tested using logistic regression.	Significant beneficial effect of MMN fortification on change in all markers of iron and vitamin A status, Hb levels, iron deficiency anemia, and vitamin A deficiency ($P < 0.01$). No effects of MMN fortification on UI throughout the study; median UI significantly increased in both groups.	None	None	None	Effectiveness study: intervention product (salt) distributed to households, consumption not controlled. Study carried out in area of endemic goiter. Diet high in phytic acid, low in ascorbic acid, therefore low iron absorption. Groups similar at baseline. No adjustments of analyses for demographic and baseline values.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HAZ, height-for-age z-score; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; IQ, intelligence quotient; MMN, multiple-micronutrient; MUAC, middle-upper-arm circumference; NIMHANS, National Institute of Mental Health and Neurological Sciences; OR, odds ratio; PGI, Post Graduate Institute of Medical Education and Research; RR, rate ratio; UI, urinary iodine; WISC, Wechsler Intelligence Scale for Children; WHZ, weight-for-height z-score; WAZ, weight-for-age z-score; VAD, vitamin A deficiency.

Eight of nine studies assessing indicators of iron status detected a beneficial effect of MMN fortification on iron status, including the study with well-nourished Australian children. The only study that did not find an effect provided 5 g of elemental iron via an MMN powder added to the school lunch.⁶⁶

Among six studies that investigated the effect of MMNs (including zinc) compared to unfortified food interventions on zinc status, only two studies found a significant beneficial effect.^{66,67} After 16 and 31 weeks of intervention, respectively, zinc levels adjusted for baseline zinc values were significantly higher and odds of zinc deficiency significantly lower in the MMN group compared to the control group. Nga et al.⁶⁷ estimated an intervention effect of 0.61 (95% CI: 0.25–0.95) $\mu\text{mol/L}$ plasma zinc and reduced odds of zinc deficiency at follow-up in the intervention group (odds ratio [OR]: 0.52; 95% CI: 0.36–0.76). Winichagoon et al.⁶⁶ reported higher levels of serum zinc in the intervention group, with a mean difference at follow-up of 0.34 $\mu\text{mol/L}$ (95% CI: 0.08–0.60) and reduced odds of deficiency at follow-up (OR: 0.63; 95% CI: 0.42–0.94). Abrams et al.⁶⁸ also found that the prevalence of zinc deficiency at follow-up was significantly lower in the MMN group (4.6%) compared to the control group (14.5%) ($P < 0.05$). However, baseline data on zinc status was not reported. Therefore, no judgment can be made on whether the change was due to the MMN intervention. Other studies comparing interventions with MMNs to those with unfortified food did not find any effect on biochemical zinc status or deficiency,^{63,69} not even in a population with a high prevalence of zinc deficiency.⁶³ Across all studies, zinc was included at relevant dosages of 2.3–7.5 mg per day.

All five studies evaluating iodine status found a beneficial effect of MMN fortification on urinary iodine excretion levels or concentrations of thyroid-stimulating and parathyroid hormones. However, two studies that also assessed prevalence of goiter did not find any effect of MMN fortification after either a 12- or a 14-month intervention period, despite a high prevalence at baseline.^{70,71} One study also looked at the effects of MMN fortification on prevalence of other clinical symptoms of micronutrient deficiencies (i.e., Bitot's spots, bleeding gums, glossitis, cheilosis, and angular stomatitis).⁷⁰ In the experimental and control groups, the prevalence of these symptoms was less than or equal to 6% at baseline and nearly absent after 14 months, but there was no difference in prevalence between the groups at either time point.

The study that compared MMN-fortified salt to iodized salt measured a greater positive impact in the intervention group for all of the biochemical markers of nutritional status that were assessed, i.e., Hb, vitamin A, iron, and iodine status.⁷⁶

Effects on anthropometric status

Seven studies investigated the effects of MMN-fortified foods compared to unfortified foods on anthropometric outcomes, mainly height, weight, and prevalence of undernutrition (Table 3). Four of the seven studies found significant beneficial effects on weight and BMI; on average, children in the MMN-fortified group gained between 0.47 and 0.56 kg more weight than controls and their gains in BMI compared with controls were 0.23–0.35 kg/m^2 greater.^{68–70,72} Two of seven studies found a significant beneficial effect on height gain, with mean differences of about 0.6 to 1.0 cm in height increments between the groups after 6 or 14 months, respectively.^{70,72} One of the studies also reported a significantly greater increase in absolute fat-free mass (mean difference [MD], 0.9 kg), percentage of body fat (MD, 0.81%), and whole-body bone mineral content (MD, 22 g) compared to controls.⁷³ This 14-month intervention supplied a fortified milk porridge that provided extra vitamin D and calcium together with other micronutrients. The other three studies did not find any effects on height or weight.^{64,71,74}

Effects on morbidity outcomes

Seven studies investigated the effect of MMN-fortified foods compared to unfortified foods on morbidity outcomes (Table 3). Two studies that assessed the effects of MMN fortification on respiratory- and diarrhea-related illness reported a beneficial effect.^{73,74} Van Stuijvenberg et al.⁷¹ reported fewer school absences attributed to respiratory- and diarrhea-related illness over a 1-year period in the MMN-fortified group compared to the control group, 33 versus 47 missed days per 100 children for respiratory- ($P = 0.097$) and 52 versus 79 missed days for diarrhea-related diseases ($P = 0.013$). Manger et al.⁷⁴ found that children receiving MMN powder for 31 weeks had a significantly lower incidence of respiratory-related symptoms and diarrhea compared to children in the control group, with rate ratios of 0.83 (95% CI: 0.73–0.94) and 0.38 (95% CI: 0.16, 0.90), respectively. No difference between the groups was seen for incidence of fever, other diarrhea-related illnesses (vomiting, nausea, and stomach pain), or the duration of morbidity episodes for respiratory-related diseases, such as runny nose and cough. A third study did not find any beneficial effect of fortification on the incidence of diarrhea, fever, cough and cold, or ear infection, but the reported episodes of any illness were, on average, 2.4 days significantly shorter in the MMN-fortified group compared to the control group.⁷⁰

One study evaluated the impact of MMN fortification on physical fitness and heart rate,⁶⁴ and one study each looked at the following secondary outcomes:

parasitic infections,⁶⁷ stool bacteria load,⁶² inflammation,⁶⁹ and white blood cells.⁷¹ Nga et al.⁶⁷ reported that MMN fortification did not have an independent effect on parasitic infection but it interacted positively with de-worming treatment: The prevalence of parasitic infections was found to be reduced to a greater extent in children who received MMN-fortified biscuits in addition to de-worming treatment compared to children who received de-worming treatment and unfortified biscuits. Significantly higher amounts of total bacteria, bifidobacteria, and bacteroides were reported in the stools of children who had received MMN-fortified milk for 3 months compared to children who had received regular unfortified milk.⁶² In this study, the intervention product was fortified with inulin and taurine as well as MMNs. The remaining studies did not provide conclusive data on markers of immune capacity or response.

Effects on cognitive outcomes

Seven studies investigated the effects of MMN-fortified foods compared to unfortified foods on cognitive abilities; among them were four studies that also investigated changes in academic performance (Table 3). Three studies found significant beneficial effects of MMN-fortified beverages compared to unfortified beverages on memory tests: one study found that visual recall of familiar objects – as measured on a scale from 0 to 15 – improved on average by 0.5 points more⁷⁴; one study reported that a cluster of outcomes from auditory verbal memory test improved significantly more with an estimated effect size of 0.23 standard deviation (95% CI: 0.01–0.46)⁶³; and one study reported one statistically significant positive finding (in a set of nine cognitive outcomes) on working memory.⁷¹

Four studies found mixed results or no beneficial effects on cognition or academic performance. Osendarp et al.⁶³ (Indonesia sample) did not find effects in the overall study population, but in subgroup analyses, a positive effect on verbal learning and memory was observed in girls but not in boys. Solon et al.⁶⁴ did not find an overall effect in the population but found some beneficial effects of the MMN intervention on verbal, non-verbal, and total cognitive scores in a rather small sub-sample of children with anemia (Hb < 11 g/dL) at baseline. Vazir et al.⁷⁵ reported only two significant findings on tests assessing attention and concentration from a set of about 20 standard cognitive tests and three academic tests: 1) a positive effect of MMN fortification on performance in a Knox-test; 2) a negative effect (unfortified > MMN-fortified) on letter cancellation. Lien do et al.⁶² did not report any significant effect of the MMN-fortified food versus unfortified foods on any of

the outcomes in a small set of three standard tests on working speed, efficacy, and working memory.

RELEVANCE AND LIMITATIONS OF LITERATURE REVIEW

Overall, the studies in this review found that MMN fortification resulted in positive effects on biochemical indicators of micronutrient status and reduced anemia prevalence compared to unfortified foods or food fortified with a single micronutrient. Eight of ten studies consistently reported that MMN fortification improved iron and Hb status. Only one study, conducted among well-nourished Australian children who had adequate Hb levels at baseline, found no effect of MMN fortification on Hb status.⁶³ Another study that did not find an effect on iron status provided iron at a relatively low dose (5 mg per day) in a form with low bioavailability (elemental iron) via a seasoning powder added to school lunch.⁶⁶ The fortified food interventions that did improve iron status provided between 5 mg and 14 mg of iron daily in a variety of chemical forms for at least 8 weeks.

Beneficial effects of MMN fortification on iodine, vitamin A, and B vitamin status were reported repeatedly, yet, only two of six studies observed a positive effect on zinc status. This could be due to poor absorption of zinc, possibly related to the combined fortification of zinc with iron at a ratio ranging from 1:1 to 1:3. Previous research suggested that combined supplementation with iron and zinc can lead to a smaller effect on biochemical and functional outcomes than supplementation with either nutrient alone. It has been postulated that zinc and iron may interact in such a way that they compete for transporters necessary for absorption, but the evidence is conflicting and there is not enough evidence to discourage joint administration.⁷⁹ In both studies that measured a significant beneficial effect on serum zinc levels, less than 5% of the study participants had low iron stores at baseline, whereas more than 50% had low levels of zinc in serum or plasma.^{66,67} Absorption of zinc could also have been reduced due to a high phytate content of the carrier food or the general diet. Otherwise, the equivocal effects on zinc could be attributed to the low reliability of serum or plasma zinc as an indicator of individual zinc status.

Though iodine status, as well as concentrations of thyroid-stimulating hormone and parathyroid hormone, was consistently shown to improve upon intervention with MMN fortification, no effects were seen on the prevalence of goiter after 12 or 14 months of intervention.^{70,71} While low urinary iodine excretion (<100 µg/L) is a sign of mild iodine deficiency, goiter is a clinical symptom of iodine deficiency disorder resulting from prolonged iodine deficiency.⁴ The results suggest that the dosage (75–120 µg iodine) and/or the duration of

the intervention was sufficient to reduce mild iodine deficiency but not enough to reverse advanced iodine deficiency and/or to reduce the enlargement of the thyroid gland.

While the positive impact on short-term nutritional outcomes was rather consistent (with the exception of zinc), these improvements did not always translate into a measurable impact on functional health outcomes of growth, morbidity, and cognitive development. While four of seven studies reported a significant beneficial effect of the MMN fortification on weight gain, increased BMI,^{68–70,73} or MUAC,^{68,69} only two studies showed an effect on height.^{72,73} A possible explanation for a lack of a clear effect may be that the extra energy and macronutrients, which were also provided to the control group, contributed to the height and weight gains observed in both groups and might have masked any additional effect of the MMNs. This may be all the more relevant if children were initially undernourished, as was the case in many of the reviewed studies. Interventions that positively impacted child growth provided an MMN combination of at least iron, vitamin A, zinc, iodine, B-vitamins, and vitamin C via fortified beverages (3 studies) or milk porridge (1 study). While effects on linear growth were observed after intervention periods of 6 and 14 months,^{72,73} effects on weight gain were already reported after 8 weeks of intervention.⁶⁸

The effects of MMN fortification on morbidity outcomes were equivocal, with four of seven studies showing some beneficial effects on children's health. The most common effects observed were reduced incidence or duration of diarrhea and respiratory-related diseases after MMN fortification. Since respiratory and diarrheal diseases are probably the most common illnesses in children, it might have been easier to detect an effect on these illnesses compared to other less-common diseases. The effects of MMN fortification on other diseases or health outcomes were assessed only by single studies, and more evidence is needed to draw conclusions.

Overall, the results of MMN-fortified food interventions on children's cognitive performance were inconsistent and differed by cognitive domain. The cognitive abilities most affected relate to working memory, with four of six studies reporting some beneficial effect. The two studies that clearly found a beneficial effect of MMN-fortified foods compared to unfortified food on working memory performance in the entire sample of participants had in common a long duration (6 and 12 months) and delivery of iron and vitamin A in combination with iodine and/or zinc.^{63,74} Other effects on memory and attention/concentration, as reported by two more studies, might be chance findings given the many outcomes assessed at follow-up and few significant differences between groups.^{71,75} The consistent positive results on

working memory across studies suggests there may be a valid effect of MMN fortification.

The present review offers a comprehensive and concise overview of the experimental research on the impact of MMN food fortification on the nutrition and health of school-age children. All of the studies reviewed were efficacy studies carried out in well-controlled settings. The interventions, however, varied with regard to the combination of micronutrients, the dosage, duration of intervention, and potential confounders and effect modifiers (e.g., the age and nutritional status of the study population or the macronutrient content of the fortified food). Also, the methods applied to assess health outcomes varied across studies. The cognitive tests and their psychometric properties were not always well described. Due to this heterogeneity it is challenging to compare results across studies.

To our knowledge, this review is the first to show that provision of MMNs via fortification consistently improves biochemical indicators of micronutrient status in schoolchildren. Whereas a previous Cochrane systematic review that investigated the effectiveness of school feeding without MMN fortification reported mixed results on Hb or hematocrit,⁶⁰ this review provides clear evidence of the benefits of MMN fortification for reducing anemia prevalence in school-age children.

The same Cochrane review on the effects of (unfortified) school meal interventions reported small improvements in height and/or weight gain of schoolchildren. The present review suggests that MMN-fortified food might have a beneficial effect on growth, especially weight gain, compared to unfortified food, though the results are equivocal. This review's findings of a possible positive effect of MMN fortification on weight are in line with an earlier meta-analysis that investigated the effects of MMN fortification on child growth.⁴² The meta-analysis included five studies in infants and children above the age of 5 years and showed an overall weighted effect size of MMN of 0.28 (95% CI: 0.16–0.41) for height and of 0.28 (95% CI: -0.07–0.63) for weight. The present review reports on two additional studies that further strengthen the hypothesis that MMN fortification may cause healthy weight gain in school-age children.

The earlier Cochrane review on (unfortified) school feeding interventions as well as a meta-analysis on the effects of MMNs on cognitive performance reported beneficial effects on fluid intelligence (i.e., reasoning ability) and academic or math performance.^{55,60} No effect of MMN fortification was found on these particular cognitive domains in the present review. The inconsistency of the findings reported here is mostly due to methodological issues: few of the studies in the present review used batteries designed to assess fluid intelligence^{63,75} and academic performance as a separate outcome^{74,75} (none of

them showing any significant effect of the intervention), whereas the Cochrane review⁶⁰ and the meta-analyses⁵⁵ involved many more trials (up to 12) measuring these abilities instead. In contrast, most of the studies reviewed here measured some aspects of working memory and learning, making it more likely that some effects would be detected. It is supposed that the absence of findings on fluid intelligence and academic performance are at present explained by the lack of available data. Future research should continue to investigate the cognitive functions of fluid intelligence, memory, and academic performance (mostly mathematics and reading).

MMN interventions might improve children's growth more than interventions with single nutrients, as shown by a meta-analysis of Ramakrishnan et al.⁴² Furthermore, a study investigating the effects of a micronutrient intervention in 6–9-year-old Chinese schoolchildren reported that cognitive performance and growth improved significantly more after treatment with zinc plus a combination of MMNs compared to treatment with zinc alone.^{80,81} These findings suggest that multiple growth-limiting nutrient deficiencies may exist simultaneously and can be relieved by MMN interventions rather than by single-micronutrient supplementation. Another possible explanation for why the provision of MMNs can be more effective than single micronutrients may be related to the interaction of micronutrients. Micronutrients such as vitamin A, zinc, and iron interact with each other in such a way that inadequate intake of one micronutrient can negatively influence the absorption, metabolism, or depletion of other micronutrients.^{82,83}

School feeding programs are widely popular in most of the world and, by virtue of the fact that they provide food for direct consumption to the child, offer a ready vehicle for delivering missing micronutrients to schoolchildren through fortification. With MMN fortification, school meals can provide a safe and effective nutritional intervention and make a valuable contribution to the nutritional needs of schoolchildren.^{84–87} MMN fortification may offer logistical advantages to supplementation with single micronutrients in the context of school feeding programs. Fortified foods and on-site fortificants such as powder and salt may be more acceptable to children compared to liquids or tablets, and the provision of multiple micronutrients at physiologic doses reduces the risk of overdose, thereby eliminating the need for precise targeting and routine monitoring of costly biochemical indicators. There are trade-offs, however, and MMN fortification at lower doses may not result in as great an impact on children's health as supplementation with higher doses of a single nutrient. At present, micronutrient supplementation is not commonly recommended for school-age children. The only guidance from the WHO that pertains to

school-age children calls for supplementation with iron when anemia prevalence is >40% in this age group and there is no food-based strategy, such as dietary modification or fortification, in place to improve iron status.⁸⁸ The findings reported here that MMN fortification of foods may be useful for school feeding should not be considered to override any WHO-recommended micronutrient supplementation interventions for preschool or school-age children. The decision to implement targeted micronutrient supplementation, MMN-fortified food, or on-site fortificants will always need to be context specific.

CONCLUSION

The findings of this review show that MMN food fortification can improve micronutrient status and reduce anemia in schoolchildren. MMN fortification also seems to be effective for reducing morbidity from diarrhea and respiratory infections and might have positive effects on child growth and cognitive domains, particularly those related to memory. Future research on the impact of fortification on health and developmental outcomes should test the efficacy of MMN-fortified-food-based interventions in a two-by-two design (testing MMN fortification of food against an unfortified food, a MMN tablet, and no intervention at all) in order to be able to assess the separate effects of energy and macronutrients versus MMNs as well as their interactions. Field studies should strive to ensure rigorous assessment of outcomes based on standardized methods that are appropriate for the target population and apply valid statistical procedures. Researchers should consider comparing the cost-effectiveness of providing MMN-fortified foods to that of micronutrient supplements through schools in future studies. The results of this review show that MMN fortification of food can have an impact on various aspects of the health and development of schoolchildren. Considering the vast number of school-age children suffering from MMN deficiencies and the consequences, the overall impact of MMN interventions in school-age children can be an investment in future generations by helping these children to achieve optimal health and increase their potential to learn.

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