Review Article

Micronutrient interventions on cognitive performance of children aged 5-15 years in developing countries

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It is estimated that more than 200 million young children worldwide fail to reach their potential in cognitive development owing to undernutrition. Numerous studies have assessed the effects of micronutrient supplementation on growth and cognitive development in infants, toddlers and preschoolers. However, micronutrient interventions on the cognitive performance of older children are limited. This article seeks to provide an update on micronutrient interventions and cognitive outcomes among children aged 5-15 years in developing countries. A total of 13 randomized controlled trials published since 2000 were identified. Majority of these studies assessed the effects of micronutrient-fortified foods on various domains of cognitive function. Among key micronutrients assessed were iron, zinc, iodine and vitamin A. This review found a lack of consistency in the impact of micronutrient supplementation on intelligence, long term mental functions and school examination grades of the children. A beneficial effect of micronutrient supplementation on short term memory was more consistently reported. Overall, the evidence from this review for the impact of micronutrients on cognitive performance in older children remains equivocal. In light of the growing interest on the influence of nutrition on cognition, it is important that culturally-appropriate and sufficiently sensitive assessment tools be used for measuring the desired cognitive outcomes that are most likely to be affected by the nutrients under study.

Key Words: micronutrients, cognitive performance, children aged 5-15 years

INTRODUCTION

Undernutrition is widespread especially in developing countries despite decades of poverty reduction and food supplementation efforts. Micronutrient deficiency is generally correlated with overall undernutrition, particularly in poor households where poverty limits the quantity and quality of dietary intakes.[1] Deficiencies of iron, vitamin A, iodine, B vitamins and zinc are among the common types of micronutrient malnutrition worldwide affecting millions in low-income countries. Interactions between co-existing deficiencies of micronutrients [2] may further exacerbate the micronutrient deficiency state. Such deficiencies can have long-term health consequences, including impairment of neurobehavioral function.[3]

The following section serves as a backdrop for the aim of this article, which is to provide an update on micronutrient intervention studies published since 2000.

Micronutrient interventions on cognitive performance in children: review of studies published before 2000

The psychosocial development of children consists of several interdependent domains, including sensory-motor, cognitive, and social-emotional functioning. Micronutrient deficiencies are known to affect these developmental processes and functions, resulting in negatively shifting the intelligent quotient (IQ) potential of children.[4,5] Associations between macronutrients and poor mental and motor developmental levels in early childhood have often been reported, especially in low income communities.[6,7] For example, in Egypt, intake of calories, protein and fat was found to be associated with mental development of toddlers at 24 months.[4] However, Grantham-McGregor and Baker-Henningham [8] observed that, while such an association exists, it is likely to be confounded by socio-economic factors. Undernourished children generally come from a poor background characterized by poor housing and sanitation, exposing the children to frequent infections, and inadequate health and nutritional care. These factors may independently affect children's cognitive development and thus, it is difficult to infer a causal relationship between under nutrition and development from observational studies.

Some of the earlier single micronutrient interventions on cognition focused on iron supplementation, reflecting the serious magnitude of iron deficiency worldwide then and now. Iron interventions, conducted mostly in the 1980s and 1990s, showed a positive effect of iron supplementation on intellectual development (e.g. at dosages of about 100-300% of the Recommended Dietary

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Allowance).[9] This effect was particularly apparent for intelligence tests among children who were anemic at baseline or having iron-deficient anemia. A meta-analysis of randomized controlled studies (RCTs) undertaken in 1985-2005 on iron supplementation concluded that there was some positive evidence with respect to improving attention and concentration in children aged 6 years and above, irrespective of baseline iron status.[10] In anemic groups, iron supplementation improved IQ by 2.5 points but had no effect on memory, psychomotor skills or scholastic achievement. Lozoff and Georgieff [11] also showed that mental development scores were significantly lower when infants with iron-deficiency anemia were compared to those with adequate levels of iron.

These reviews indicated that iron supplementation was more effective in improving the mental development of the more vulnerable children in terms of iron deficiency. The importance of following up on the children after iron supplementation was emphasized by Grantham-McGregor and Ani [12] in a review of iron interventions conducted in 1978-2000. Since child development changes over time, benefits of treatment or detrimental effects may appear at an older stage of development.

Besides iron, zinc interventions also have shown beneficial effect on childhood mental development, especially at an early stage including preterm infants.[13] In Chile, infants from poor families who received 5 mg of elemental zinc daily for 1 year had higher scores in motor quality (gross and fine-motor movement and control), than the control group, but there were no differences in the children's mental or motor scores on the Bayley Scales.[14] Low birth weight infants benefited from consuming a formula fortified with zinc in showing better growth and motor development than those on no-zinc formula.[15]

Nonetheless, there appears to be a lack of clear consensus on the potential positive influence of zinc supplementation on the cognitive functioning of older children. In reviewing zinc supplementation studies carried out among school-age children in the 1990s, Black *et al.,*[16] reported that one study found no effect, while two trials in urban Chinese and Mexican-American reported beneficial impact. In the latter studies, zinc supplementation showed superior neuropsychological processes, particularly attention and reasoning. Zinc combined with other micronutrients may exert a greater influence on cognitive function than when zinc is administered by itself.[17]

As micronutrient deficiencies often coexist and may synergistically affect cognition, supplementing children with multiple micronutrients has been a more popular intervention than single micronutrient supplementation. In a systematic review of RCTs, published in 1970-2008, on multiple micronutrient supplementation for improving cognitive performance in children, Eilander *et al.*,[18] reported a positive increase, albeit marginal, in fluid intelligence, which is associated with reasoning abilities, but not with crystallized intelligence that reflects acquired knowledge. A similar finding was reported by Benton *et al.,*[19] in that a positive effect of micronutrient supplementation was mostly for non-verbal measures, but not for verbal intelligence, which depends on acquired knowledge. Table 1 summarises the roles of some key macro- and micronutrients implicated in brain functions and mental performance.

In comparison to the abundance of studies on the effect of micronutrient supplementations on improving morbidity, physical growth and nutritional status of young children,[20-25] there are relatively fewer studies that investigated the impact of micronutrients on cognitive functions of older children.

METHODS

This paper aims to provide an update on the effects of micronutrient interventions, whether by supplementation or food fortification, on the cognitive performance of children aged 5-15 years in developing countries. Children of this age group are growing rapidly, experiencing pre-puberty and puberty changes. Beside physical and physiological changes, they may also be subject to emotional, social and psychological influences in school and at home. Dietary intake may be affected under these circumstances, leading to delayed physical and cognitive development, thereby preventing children from reaching their full potential.

Selection criteria

1. Only RCTs were selected for the review.
2. We included only RCTs that assessed children aged 5-15 years. Studies that examined children outside this age range were excluded.
3. Micronutrients used were vitamins and/or minerals only. Studies that used other dietary components such as essential fatty acids, functional foods were excluded.
4. Included were RCTs that evaluated one or more developmental indicators (psychomotor development, cognitive performance, mental development, IQ, and school performance) as primary or secondary outcome measures of the interventions.
5. Studies with supplementation duration of at least four months were selected.
6. Included are RCTs conducted in countries in developing regions, as defined by the United Nations (http://unstats.un.org/unsd/methods, last revised on 20 September, 2011).
7. As this is an update review, only RCTs published after the year 2000 were included.

Search strategy

We searched in titles and abstracts of several databases including the PUBMED, Web of Science, Scopus, Science Direct, EBSCOHOST and the Cochrane Database of Systematic Reviews (CDSR). The Google Scholar was also used to search for pertinent documents based on key words.

A total of 13 RCTs that met the inclusion criteria were identified for the current review. Out of these, 9 were micronutrient-fortified foods ("food-based") and 4 micronutrient supplementation ("supplement-based"), studies. Most of the interventions were conducted in Asia, with one each in Kenya and Mexico.

RESULTS

General characteristics of the studies

A plethora of micronutrients were included in the

Table 1. Summary of the roles of key macro and micro nutrients in brain function and its impact on cognitive domains

Nutrients	Role in brain function	Effects of deficiency on cognitive domains
Glucose	provides energy for the brain	• depression[21] • affects overall mood state and psychological well-being [4]
n-3 PUFA	• may influence neural functioning through its effects on proteins/ enzymes that play a role in brain membranes [18] • neuronal gene expression [19]	• delayed information processing [21]
B vitamins	propagates nerve impulses	• depression [21] •
Thiamin, folate and vitamin B-12	• maintains the nerve's membrane potential [21] • helps in proper nerve conductance [3] • maintains integrity of the myelin sheath [21]	• episodic memory and language ability [14]
Iron	• proper development of oligodendrocytes (the brain cells that produce myelin) [5] • cofactor for several enzymes that synthesize neurotransmitters [6]	• lack of memory and learning impairment [7] • lower cognitive scores, poorer motor development [1] • altered social emotional development [15] • loss of brain iron compromises cognitive development.
Iodine	Neurocellular proliferation, synapse and dendritic formation [21]	• lower IQ scores [16] • poor cognitive abilities – verbal knowledge[16], non-verbal and verbal abstract reasoning, visual-spatial perception and executive functioning [17] • tremendous drop in intellectual ability [17] • lack of coordination and hearing impairment [8]
Zinc	• essential to the central nervous system and zinc containing neurons are concentrated in the fore-brain [20] • zinc-dependent neurotransmitters in the mossy fibres system of the hippocampus are involved in memory [21]	• deficits in attention, learning, memory, and neuropsychological behavior [9-11]

treatment groups, especially for the food-based interventions (Table 2). The types of food used as a vehicle for micronutrient fortification included biscuits, milk and beverages. In some studies, the micronutrient fortificants were added directly into drinks or cooked foods, and provided as part of school meals or consumed at home during school holidays.

The supplement-based interventions focused on comparing the effect of iron and/or zinc given on a daily or weekly basis in two of the studies (Table 3). In the other two studies, multiple micronutrients were supplemented during pregnancy through postpartum in one case and during infancy for 6 months in the other. In both cases, cognitive performance of the children in the study was assessed 7-9 years later. Some studies provided information on the proportions that the added micronutrients met the recommended daily requirements for children aged 5-15 years. A range of one-third to 100% of the recommendation values of either the WHO/FAO or those of the individual country (e.g. Thailand, Vietnam, and Indonesia) were used.

Most of the interventions were undertaken in rural communities of low socio-economic status. In such settings, the prevalence of worm infestation and undernutrition including underweight, stunting and anaemia among children were high. Many studies reported that the children were de-wormed at baseline, while those who were severely anaemic (Hb<8 g/dl) and malnourished (WAZ and HAZ < –3SD) were excluded from participation.

The sample size ranged from about 100 to over 800 comprising boys and girls. As for the duration of study, the food-based interventions tend to last longer than the supplement-based studies. More than half of the food-based studies continued for at least 12 months, compared to about 4-6 months for the nutrient-supplemented studies.

Cognitive functions tests

A diversity of tests was used to assess the different domains of cognitive performance. All the interventions assessed intelligence as an outcome, mostly using the Wechsler Intelligence Scales for Children (WISC-3, WISC-R, WISC-4 or adaptations e.g. Malin's Intelligence Scale developed for Indians) (Table 4). Nonverbal intelligence was assessed by the majority of the studies using the Raven's Colour Progressive Matrices (RCPM), or others such as the comprehensive test of nonverbal intelligence (CTONI), and the Universal nonverbal intelligence (UNIT). Nonverbal intelligence is internationally recognized as a culture-fair test of general intelligence.

Other domains of cognitive performance assessed in the micronutrient interventions were verbal learning,

Table 2. Characteristics of the micronutrient intervention studies on cognitive performance of children: food-based

Reference	Study location	n	Age (years)	Sample characteristics	Intervention	Duration of study
Gewa *et al* (2009) [26]	Eastern Kenya	529	7.6 ± 1.3 boys and girls	Rural, subsistence farming 12 primary schools randomized to one of 4 feeding groups	4 snack groups: 1) vegetarian supplement based on traditional maize, beans and vegetables ("githeri"); 2) milk supplement (githeri + 200 ml whole cow's milk); 3) meat supplement (githeri cooked in 60 g minced beef); 4) No food supplement provided. Snacks provided 250 kcal per serving daily for first 3 months, increased to 320 kcals per serving for remaining intervention.	24 mo
Nga *et al* (2011) [27]	Northern Vietnam	510	6-8 boys and girls	Rice farming communes Excluded Hb < 8 g/dL, WHZ < -3SD, BMI >2SD	4 groups: 1) fortified biscuits; 2) antihelminthic treatment; 3) fortified biscuits + antihelminthic treatment; 4) placebo antihelminthic treatment + non-fortified biscuits Biscuits fortified Fe, Zn, I_2, vit A at 50%, 50%, 35% and 60% respectively of FAO/WHO RNI; B vitamins 60-110%, vits E, K 10-40% of RNI; Each serving 30 g biscuits (133 kcals) provided daily as snack in school for 5 days/week	16 wk
Lien *et al* (2009) [28]	Northern Vietnam	454	7-8 boys and girls	Rural, at baseline anaemia (Hb < 11.5 g/dL) in 47% of fortified milk and 44% of regular milk groups	3 groups: 1) regular milk; 2) fortified milk (inulin, taurine, Ca, Fe, Zn, I_2, Mn, Mg, vitamins A, D, E, B-1, B-2 and C). Two servings of 250 ml milk daily (6 days/wk), providing 20% daily energy and 40% protein of the Vietnamese RDA.	6 mo
Kumar *and* Rajagopalan (2010) [29]	Chennai, India	123	7-11 boys and girls	Excluded Hb < 8 g/dL and > 12 g/dL; deworming at baseline, mid and end of study	2 groups: 1) residential school children given daily 1 g of multiple micronutrient food supplement (MMFS) after de-worming; 2) community day school children de-worming only MMFS contained Fe, Ca, vitamins A, C, E, B-2, B-6, B-12, folic acid, niacin and lysine.	12 mo
Vazir *et al* (2006) [30]	Hyderabad India	608	6-15	Semi-urban, middle income, residential school students; at baseline 50% of children deficient in vitamins A, C, B-12, B-2, B-6, iron	2 groups: 1) beverage fortified with multiple micronutrients; 2) placebo Vitamins: 400 µg RE vit A, 0.7 mg B-1, 1.6 mg B-2, 0.9 mg B-3, 2 mg B-6, 200 µg folate, 1 µg B-12, 80 mg C, 2.5 µg D, 400 mg Ca, 14 mg Fe, 75 µg I, 2.3 mg Zn	14 mo
Manger *et al* (2008) [31]	Northeast Thailand	569	5.5-13.4 boys and girls	Rural, low socio-economic status	2 groups: 1) fortified seasoning; 2) unfortified seasoning Fortified seasoning consisted of 5 mg elemental Fe, 270 µg vit A palmitate, 50 µg KI, 5 mg ZnSO4, per serving at one-third Thai RDA. Each group received a school lunch on each school day	31 wk
Osendarp *et al* (2007) [32] (NEMO Study Group)	Jakarta, Indonesia	384	6-10	Middle to low socioeconomic status. Excluded severely malnourished (WHZ < -3SD) or severely anemic (Hb < 8.0 g/dL)	4 groups: 1) Micronutrients: Fe, folate, B-6, B-12, vitamins A and C at 100% RDA and Zn at 50% RDA; 2) DHA + EPA; 3) Micronutrients + DHA; 4) None Fortificant mixed in a fruit flavoured drink (soy 6%) taken as daily beverage in school or at home during holidays/fasting period	12 mo
Solon*et al* (2003)[33]	Batangas, Philippines	808	7-12	Rural, 52% anaemic, 21% severe to moderately anaemic, 5% severely anaemic, 90% iodine deficient	4 groups: 1) Fortified + anthelmintic therapy; 2) fortified beverage + placebo anthelmintic therapy; 3) nonfortified beverage + anthelmintic therapy; 4) nonfortified beverage + Placebo anthelmintic therapy. Each child received 200 ml beverage twice daily Beverage fortified with vitamins A, C, E, B-2, B-6, B-12, niacin, folic acid, Fe, I_2	16 wk
Muthayya *et al* (2009) [34]	Bangalore, India	598	6-10	Low socio-economic status Not severely anemic (Hb< 8 g/dL); not severely undernourished (< 3 SD WAZ and HAZ)	4 groups: 1) high micronutrients + high n-3 fatty acids; 2) low micronutrients + high n-3 fatty acids; 3) high micronutrients + low n-3fatty acids; 4) low micronutrients + low n-3 fatty acids micronutrients: vitamins A, C, B-2, B-12, folate, Fe, Zn, I_2, Ca High or low micronutrients: 100% or 15% of RDA respectively. High fatty acids: 900 mg ALA+ 100 mg DHA; low fatty acids: 140 mg ALA. Each child given a drink for 6 days/week consisting of 65 g of the powder in 160 ml boiled water.	12 mo

Hb: haemoglobin; SF: serum ferritin; SZn: serum zinc; IDA: iron deficiency anaemia; WHZ: weight-for-height z score

Table 3. Characteristics of the micronutrient intervention studies on cognitive performance of children: supplement-based

Reference	Study location	n	Age (years)	Sample characteristics	Intervention
Sungthong *et al* (2004) [35]	Southern Thailand	397	7-13	Rural, low socioeconomic status, high prevalence of underweight Excluded severe IDA (Hb < 80 g/L and SF < 20 g/L), severe malnutrition (WHZ < 3rd percentile of Thai reference)	Baseline Hb used to identify anemic children at Hb ≤ 115 g/L for < 12 ≥ 12 years old. Interventions assigned randomly within each anemic and non-anemic stratum to 1 of the 3 treatment groups: 1) daily iron; 2) weekly iron; 3) placebo. Ferrous sulfate 300 mg (60 mg elemental Fe) tablets. Duration : 16 weeks
Rico *et al* (2006) [36]	Northern Mexico; main source of lead exposure was a metal foundry	602	6-8 Boys and girls	Baseline: mean blood lead 11.5 ± 6.1 g/dL, and 51% had levels ≥10 µg/dL. Overall prevalence of children with depleted iron stores (SF<15 µg/L) and zinc deficiency (SZn ≤ 65 µg/dL) were 21.7% and 28.9%, respectively.	4 groups: 1) Fe only; 2) Zn only; 3) Fe+Zn; 4) placebo Each tablet 30 mg ferrous fumarate and/or 30 mg ZnO; Distributed daily in school and at home during school holidays Duration: 147±15 days
Christian *et al* (2010) [37]	Rural Nepal	676	7-9 boys and girls low socio-economic status	In 1999-2001, mothers received micronutrient supplements daily from early pregnancy through 3 months postpartum. 4 groups: 1) Fe, folic acid, vit A; 2) Fe, folic acid, Zn, vit A; 3) Fe, folic acid, Zn, vit A + 11 other micronutrients; 4) placebo+ vit A only; Folic acid (400 µg), Fe (60 mg), Zn (30 mg), vitamins D (10 µg), E (10 mg), B-1 (1.6 mg), B-2 (1.8 mg), B-6 (2.2 mg), B-12 (2.6 µg), C (100 mg), and K (65 µg); niacin (20 mg); copper (2.0 mg); and magnesium (100 mg), 1000 µg retinol vit A.	Out of 3,351 live births in 2000-2001 among the 4 study groups, this cross-sectional follow-up on 676 children aged 7 to 9 years in June 2007-April 2009. The children were not given additional micronutrients other than biannual vitamin A, in accordance with the Nepalese government policy, whereby children received 200 000 IU of vitamin A biannually from 6 to 60 months of age.
Pongcharoen *et al* (2011) [38]	Northeast Thailand	560	9 Boys & girls Rural, low socio-economic status	In 1998-1999, 609 infants (4-6 months) were randomly assigned to 1 of 4 groups: 10 mg Fe ($FeSO_4$), 10 mg Zn ($ZnSO_4$), 10 mg Fe plus 10 mg Zn, or a placebo. Infants received supplements daily for 6 months.	560 children (92% of original sample) participated in the follow-up cross-sectional study in 2007-8 when the children were 9 years of age.

Hb: haemoglobin; SF: serum ferritin; SZn: serum zinc; IDA: iron deficiency anaemia; WHZ: weight-for-height z score attention, concentration and memory span. Tests such as the *Rey Auditory Verbal Learning Test* (RAVLT) were used to test for long term verbal learning and memory.

Testing for short term memory included in several of the interventions was based on such tests as the Mann-Suiter Visual memory screen for objects (picture recall test), while the Digit span backward and forward test was used by some studies as a measure of attention and concentration. Some of the interventions also incorporated school examination grades for various subjects as a measure of cognitive capability.

Main cognitive outcomes (Table 4)

Intelligence

All the 9 food-based studies had included assessing intelligence as one of the cognitive performance outcomes. Out of these, only 3 reported significantly higher scores for the group that received the micronutrient-fortified food compared to the other experimental groups. These 3 studies were carried out in Kenya,[26] and Vietnam.[27,28] The other 6 interventions did not find a significant impact on intelligence measures from consuming micronutrient fortified foods.

In the Kenyan study, the meat-supplemented group had significantly higher gains in overall intelligence scores compared with the other study groups.[26] The RCPM test score gains were found to correlate with daily available iron, zinc and B vitamins intake of the children. For the Vietnamese children who were anaemic at baseline, consuming multi-micronutrient fortified biscuits showed significantly higher Raven's scores than their counterpart given non-fortified biscuits.[27] In the other Vietnamese study, drinking micronutrient-fortified milk resulted in improvements in mental performance, and this was attributed to the availability of higher levels of iodine and/or iron in the fortified milk.[28]

Only one of the four micronutrient supplement-based interventions recorded a significant effect between the supplemented and placebo groups. Christian *et al.,*[37] reported that prenatal iron and folic acid supplementation of Nepalese mothers resulted in children with beneficial effects on intellectual functioning compared to controls. They attributed the positive finding to the widespread serious iron deficiency in young children in Nepal.

In contrast, in the Thai study,[35] children receiving weekly iron supplement or placebo showed no significant difference in IQ scores, and the authors concluded that iron supplementation alone was not sufficient to bring about improvement in cognitive function, especially in a deprived environment. The authors also reported a significantly lower IQ score for children who received daily iron than the weekly iron and placebo groups. These children showed high haemoglobin and serum ferritin concentrations. These finding raised the potentially adverse effect of daily iron supplementation on cognitive function of schoolchildren.

Attention and Concentration

Out of the 13 studies cited in this review, 6 had included assessing attention and concentration as an effect of micronutrient intervention, and of these, only 2 reported a positive effect. The study of Kumar & Rajagopalan[29] found that the multiple micronutrient food supplement (MMFS) added to school meals daily for 12 months improved significantly the attention and concentration of the children. The authors attributed this result to the marked improvement in the children's haemoglobin status. Adequate iron status is recognized to have significant beneficial effects on overall attention and concentration.[10] In the other study, Vazir *et al*[30] used global tests in assessing attention-concentration, and attributed their significantly improved result to the multiple micronutrients added to the beverage taken by the children over 14 months.

Memory

Seven of the 13 studies had incorporated testing for memory following micronutrient interventions, and of these, 6 reported a beneficial effect on short term memory. These comprised of 5 food-based and one micronutrient-supplemented interventions conducted in six different countries.

Kenyan children with a higher intake of available zinc and B vitamins showed significantly higher scores for the memory tests than those with lower intakes.[26] In rural Vietnam, children drinking one glass of regular milk or milk fortified with multiple micronutrients 6 days a week for 6 months had significantly better short-term memory scores than the control group.[28] Kumar and Rajagopalan[29] found a significant difference in the mean change scores for memory between the multiple micronutrient food supplement and control groups following intervention for 12 months. Also, children from poor northeast Thailand consuming multiple micronutrients added to school lunch for 31 weeks showed significantly better visual recall performance than the unfortified group.[38] Indonesian children consuming a multiple micronutrient-fortified drink for 12 months showed a positive micronutrient treatment effect for memory, but only in girls.[32] The long term study on maternal iron-folic acid supplementation during pregnancy through 12 weeks postpartum was also shown to confer beneficial effect on working memory of Nepalese children aged 7-9 years.[37]

Scholastic achievement

None of the four studies that had included school examination grades in assessing the effect of micronutrient supplementations reported a positive result.[30,31,33,35] Educational deficits require a long term investment into socio-economic determinants besides nutritional factors. A systemic review also did not find a positive effect of multiple micronutrient supplementations on academic performance.[18]

DISCUSSION

Deficiency of key micronutrients can have serious adverse effects on brain development, particularly during gestation and early postnatal periods, leading to impairment of neurocognitive functioning and learning problems in childhood and adolescence. The main domains of cognition often assessed for nutrient impact are executive functions, memory, attention, perception and psychomotor functions, as well as language skills.[39] Each of the cognitive domains can be differentiated into

Table 4. Main cognitive performance outcomes according to type of intervention

	Reference	Cognitive functions assessed	Main cognitive outcomes
Food-based	Gewa *et al*. (2009)[26]	7 memory tests, test for attention, concentration & intelligence (Ravens CPM)	Groups that received animal source foods (meat, milk) had higher available Fe, Zn, B_{12} and B_2 and they showed significantly better scores for RCPM (problem-solving abilities) and short term memory and concentration tests than other groups.
	Nga *et al* (2011)[27]	Raven's Colored Progressive Matrices test (CPM); Wechsler Intelligence Scale (WISC III)	Children anaemic at baseline receiving fortified biscuits had significantly higher Raven's scores than children given non-fortified biscuits; no statistical effect of consuming fortified biscuits on Raven's scores in children non-anaemic at baseline.
	Lien *et al* (2009)[28]	4 tests: 1) Raven's CPM; 2) verbal meaning test; 3) arithmetic test; 4) Digital Span tests	Milk drinking children showed significantly better results for mental tests than control group; fortified milk children showed superior performance for short term memory than regular milk group
	Kumar *and* Rajagopalan (2010)[29]	7 memory tests, test for attention, concentration & intelligence (Ravens CPM)	In the memory tests and test for attention, the mean change in scores in experimental group was significantly better than control group. No significant improvement in the overall intelligence between the two groups
	Vazir *et al*. (2006)[30]	Malin's Intelligence Scale (Indian adaptation of WISC III); PGI Memory Scale; tests on attention and concentration; academic scores	Fortified group showed significant improvement for tests on attention and concentration; other tests on IQ, memory and school exam scores did not show significant differences between the 2 groups.
	Manger *et al*. (2008)[31]	Test for short-term learning, memory and attention span: WISC-III),Visual Recall test and school grades	Significant differences between groups for visual recall scores (visual memory)
	Osendarp *et al* (2007)[32] (NEMO Study Group)	(WISC-III): verbal and performance; Rey Auditory Verbal Learning Test (RAVLT) Visual attention (NEPSY);	No significant treatment effects observed on any cognitive test outcomes after 12 months of intervention. Significant effect for verbal learning and memory in girls only.
	Solon *et al*. (2003)[33]	Written Primary Mental Abilities Test (PMAT-FC) consisting of verbal, non-verbal test; quantitative assessment	Significant changes for Fe def. anemia and I_2 def. children for verbal and non-verbal ability. Fortified groups showed no significant changes in total cognitive performance at 0 and 16 weeks
	Muthayya *et al* (2009)[34]	11 subtests comprising 6 KABC II, 2 WISC-R and 3 RAVLT tests; tests conducted at baseline, 6 and 12 months	All groups had a significant improvement; high MN more beneficial than low MN at 6 months but not at 12 months; no significant differences between high and low n-3 fatty acids treatment. Overall, high MN as effective as low MN on cognitive performance
Supple-ment- based	Sungthong *et al*. (2004)[35]	Test of Nonverbal Intelligence (TONI-2); school exam marks	IQ score increased in all groups compared to baseline; however, IQ change in daily Fe group was sig less than weekly Fe and placebo groups.
	Rico *et al* (2006)[36]	Wechsler Intelligence Scale for Children-Revised Mexican version [WISC-RM] and Peabody Picture. Vocabulary Test	Performance on all tasks improved significantly over time but not related to the supplementation.
	Christian *et al* (2010)[37]	Universal Nonverbal Intelligence Test (UNIT); tests of executive function; motor functions using the Movement Assessment Battery for Children (MABC), finger tapping test	Intellectual functioning memory, motor functioning positively associated with prenatal Fe & folic acid supplementation in Nepal; ; no sig differences between control and groups given (Fe, folic acid & Zn) or multiple micronutrients
	Pongcharoen *et al* (2011)[38]	WISC III (verbal & nonverbal abilities); Raven's Colored Progressive Matrices (CPM) (nonverbal); school performance scores	No significant differences in any of the cognitive outcomes between the 4 groups. Supplementation Fe or Zn or both during infancy does not lead to long-term cognitive improvement.

specific cognitive functions e.g. short term and long term memory functions. Thus, the challenge arises for researchers as there are available numerous potential cognitive outcome measures for assessment. The researcher needs to apply appropriately sensitive assessment tools to measure the outcomes most likely to be affected by the test nutrient or food product.

Researchers in this review were found to use a variety of assessment tests to measure the same domain: intelligence. While some used global measures of intelligence, others used cognitive test developed by own institutions e.g. Hanoi National University of Education,[28] National Institute of Mental Health and Neurological Sciences (NIMHANS), Bangalore,[34] and the Primary Mental Abilities Test for Filipino Children.[33] Results from such a variety of outcome measures poses a challenge in making comparisons, and the applicability of one result may be limited to populations without a similar deficiency.

In this descriptive update, the RCTs-based micronutrient supplementation interventions showed a lack of consistent impact on intelligence and long term mental functions among children aged 5-15 years. Some of the study periods may be too short for the supplementation to bring about significant differences in acquired skills and knowledge following the nutritional intervention. As suggested by Benton,[19] verbal intelligence comprises the acquired knowledge that might not be affected by nutrition on the shorter term. Failure to generate significant changes in the intelligence tests may also be due to the fact that the study children were already performing well and additional micronutrients were not able to stimulate further increases in the IQ tests.[30]

In contrast, a beneficial effect of micronutrient interventions on short term memory was demonstrated by several of the studies using food fortified with multiple micronutrients. It appears that multiple micronutrients may have a synergistically positive influence on the hippocampus, which is known to play a critical role in the encoding and retrieval of novel information in short term memory.[40]

The issue of multiple versus single micronutrient supplementation on childhood mental development requires more studies. While a study in India had reported no significant effects of multiple micronutrient interventions on motor and mental development among preschool children,[41] Allen *et al* [42] reported an overall evidence of multiple micronutrient intervention significantly improving young child motor development as compared to interventions using 0-2 micronutrients. It is suggested that the magnitude of the effect of multiple micronutrient interventions may be contextual, depending on the prevalence of different micronutrient deficiencies and/or infections such as HIV and malaria.[43]

The effect of prenatal micronutrient supplementation on improved cognitive effect at an older age has received increasing attention.[44] There is limited evidence showing benefits are more likely to be sustained if supplementation begins in late pregnancy or at birth and is continued until the child is at least 24 months old.[8] In this review, in utero iron plus folic acid supplementation had a significant beneficial effect on intellectual, executive, and some aspects of motor functioning.[31] However, adding other nutrients to the maternal supplement, including zinc, or supplementation during preschool years with iron and zinc supplementation followed by maternal iron plus folic acid did not bring about additional benefit to any of the developmental outcomes.[44]

Overall, the evidence shown in the review remains equivocal for the impact of micronutrients on cognitive performance in children aged 5-15 years. More RCTs should be conducted in developing countries to provide more conclusive evidence of the impact of micronutrients on improving cognition in school-aged children. Ensuring good nutrition in early life is akin to “building cognitive reserve and is a means of decreasing the risk of cognitive decline during aging”.[18]

AUTHOR DISCLOSURES

My co-author and I declare that we have no conflicts of interest in preparing this manuscript.

The corresponding author conceptualized the article, conducted the literature search, and prepared the article; the co-author contributed in the literature search and the preparation of the article.

This is a review article and as such does not require ethical approval from our institution, the International Medical University, Malaysia.

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Review Article

Micronutrient interventions on cognitive performance of children aged 5-15 years in developing countries

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開發中國家 5-15 歲孩童在微量營養素介入後的認知功能表現

據估計，全球有超過 2 億的幼童由於營養不足導致認知功能發育遲緩。目前已有許多研究，致力於評估微量營養素的補充，對於嬰兒、幼童及學齡前兒童成長及認知發展的影響。然而，微量營養素對於較大兒童認知表現的研究則有限。本文旨在提供關於微量營養素介入對於開發中國家 5-15 歲孩童認知影響的最新研究結果訊息。自 2000 年開始，共有 13 篇隨機對照試驗結果發表。大多數研究評估微量營養素強化食品對於不同認知功能領域的影響。被評估的主要微量營養素包括鐵、鋅、碘及維生素 A。此次回顧發現，微量營養素補充的介入研究，在兒童的智力、長期心智功能及在校成績的影響結果並不一致。只有在短期記憶的部分，具有正向且較一致性的研究結果。整體而言，微量營養素對於較大兒童認知表現的影響，仍不明確。有鑑於，營養對於認知發育的效應越來越受重視，因此有必要建立適合各族群以及具足夠敏感度的分析工具，以測量最有可能受到欲研究的營養素影響之認知表現。

關鍵字：微量營養素、認知表現、5-15 歲孩童