ISSN: 2639-4391

MEDDOCS Open Access Publisher

Annals of Epidemiology & Public Health

Open Access | Review Article

Brain Nutrients: Cerebral Metabolism and Micronutrients

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Abstract

Optimal cognitive capacity is vital throughout all stages of life. Most notably a healthy nutrition in childhood and adolescence is crucial for brain development and cognitive performance. Micronutrients are an essential component of several general cellular functions as well as of functions to neurologic activity such as the synthesis of dopamine, serotonin, and myelin formation. An adequate dietary supply with brain active micronutrients, such as vitamins, minerals and omega-3 long-chain polyunsaturated fatty acids is therefore in school children of essential significance. The possibilities and limitations to boost the cognitive capacity of children for the purpose of a "brain doping" will be discussed.

Received: Jun 01, 2020

Accepted: Jul 06, 2020

Published Online: Jul 08, 2020

Journal: Annals of Epidemiology and Public health

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Brain; Diet; Vitamin D; n-3 fatty acids; Iron; B vitamins.

A healthy diet: A concept foreign to many school children

Despite numerous information campaigns in recent years, there is still a very wide gap between a healthy diet in theory and the actual eating habits of many age groups, especially children and adolescents. This has once again become alarmingly clear from the results of the HELENA study, carried out across Europe on adolescents aged 12.5 to 17.5 years. The multicentre European project was conducted in 10 countries: Belgium (Ghent), Germany (Dortmund), France (Lille), Greece (Athens, Heraklion on Crete), the United Kingdom (Birmingham), Italy (Rome), Austria (Vienna), Hungary (Pécs), Sweden (Stockholm) and Spain (Zaragoza) [1,3].

Table 1: Comparison of the eating habits of adolescents (HELENA study) with the FKE (Research Institute for Child Nutrition) recommendations for an age-appropriate balanced diet [1,3].

Food	HELENA study[1]	Balanced diet (FKE)[2]
Meat, processed meat (g/day)	160	65/75 (f/m[1])
Fruit (g/day)	125	260/300 (f/m)
Vegetables (g/day)	100	260/300 (f/m)
Fish (g/week)	20	100/100 (f/m)
Milk, dairy products (mL/day)	260	425/450 (f/m)
Drinks		
Water (mL/day)	728	1200/1300 (f/m)
Soft drinks containing sugar (mL/day)	303	[3]
Luxury food		
Chocolate (g/day)	25	[3]
Cakes and sweet pastries (g/day)	55	[3]
Total energy		
kcal/day	up to 3300	2200/2700 (f/m)[2]

[1] Age group: 12.5 to 17.5 years;

[2] Age group: 13 to 14 years

[3]Tolerated foods: according to the FKE, 10% of the total energy may be covered by tolerated foods. For the age group 13-14 years, this means ≤ 220/270 kcal/day (m/f), i.e. each 100 kcal = 45 g fruit tart *or* 4 biscuits *or* 30 g fruit gummis *or* 20 g chocolate *or* 10 crisps *or* 1 glass (200 mL) of soft drink.

According to the HELENA study, Europe's youth consume a daily average of about 160 g meat, 125 g fruit, 100 g vegetables, 55 g cake and sweet pastries, 25 g chocolate, 728 mL water, 260 mL milk, and 303 mL soft drinks sweetened with sugar. The high consumption of luxury foods and sugar-containing soft drinks is sometimes associated with a daily calorie intake of upto 3300 kcal (see **Table 1**) [1-3]. In this context, it is of interest that recent study results confirm that an unhealthy diet of this nature together with overweight is associated with shrinkage of entire areas of the brain (e.g. the hippocampus) and impaired cognitive function in adolescents [4,5]. As a result of the high-energy, but nutrient-poor intake, the total energy consumption of the majority of adolescents is above the age-appropriate optimally balanced diet as recommended by the Research Institute for Child Nutrition (FKE) in Dortmund, Germany. For example, they recommend a daily intake of 2200 kcal for 13- to 14-year-old girls and of 2700 kcal for boys of this age. A greater intake of fruit and vegetables is associated with a greater supply of vitamins (e.g. vitamin C, folic acid), minerals (e.g. calcium, potassium), phytochemicals (e.g. carotenoids) and dietary fibre. It is hardly surprising, therefore, that the number of overweight children in our country is steadily increasing and that many young people do not have an adequate dietary supply of essential vitamins, minerals, long-chain omega-3 fatty acids (e.g. eicosapentaenoic acid, docosahexaenoic acid) and other brain nutrients.

Vitamin D for the healthy development of the brain

A good vitamin D status [25-dihydroxy vitamin D (25(OH)D): 40-60 ng/mL or 60-150 nmol/L] is of key importance to child development and maturation, especially during pregnancy and growth phases. Vitamin D is therefore particularly important for the development and functioning of the brain. In its hormonally active form 1,25(OH)$_2$D, the sunshine vitamin acts as a neurosteroid through its interaction with vitamin D receptors (VDRs) during neuronal differentiation and maturation, whereby it regulates the production of neurotrophic factors such as Glial Cell-Derived Neurotrophic Factor (GDNF). 1,25(OH)$_2$D also has a marked neuroprotective effect, in that it inhibits neuronal inflammatory reactions and oxidative processes (see **Figure 1**).

VDRs are expressed in various parts of the brain, including the basal forebrain, the caudate nucleus and putamen, cerebellum, lateral geniculate body, cingulate gyrus, hypothalamus, prefrontal cortex, substantia nigra and the thalamus. The enzyme 25(OH)D 1- alpha hydroxylase, which is responsible for the conversion of 25(OH)D into its hormonally active form 1,25(OH)$_2$D, can be found together with VDRs in many regions of the brain (e.g. the hippocampus). In addition, it has been shown that VDR gene polymorphism is associated with a decline of cognitive function and the risk of neurodegenerative diseases (e.g. Alzheimer's disease) [6-8].

Today we assume that 1,25 (OH)$_2$D, in interaction with VDRs, regulates more than 2000 of the 20,488 genes in the human genome, either directly or indirectly. Besides disorders of bone mineralisation that may lead to rickets in children and osteomalacia in adults, vitamin D deficiency (serum 25(OH)D < 20 ng/mL) contributes to the pathogenesis of many chronic diseases. These include autoimmune diseases (e.g. multiple sclerosis), cardiovascular diseases (e.g. high blood pressure, heart failure), cancer and neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease).

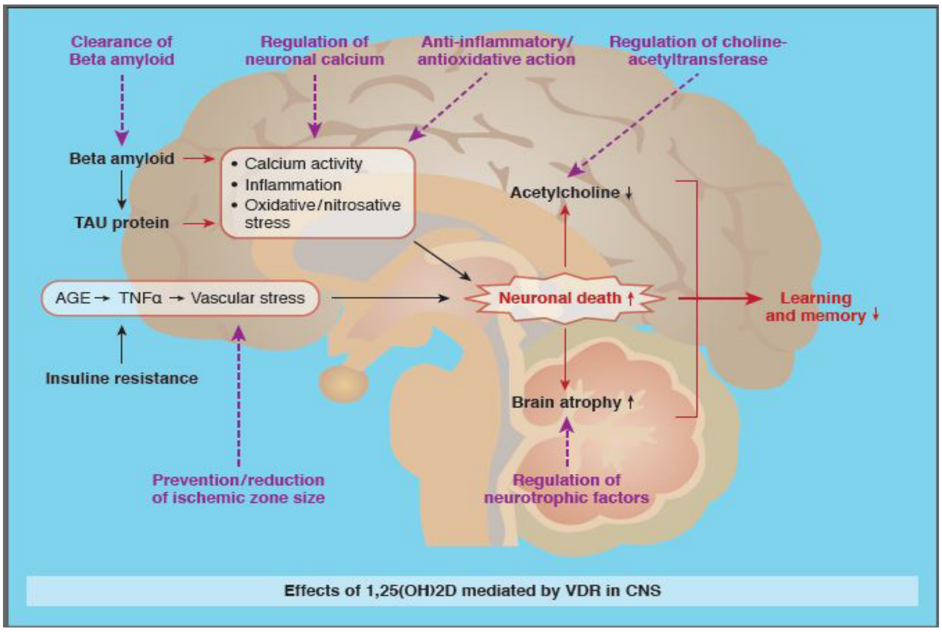

Figure 1: Effects of 1,25(OH)2D mediated by VDR in CNS.

The results of large-scale studies have shown that the vitamin D intake of most children and adolescents in Germany is worse than deficient. A representative sample of the child and adolescent health survey (KIGGS) showed that average 25(OH)+D levels in children aged 0–2 years were 23 ng/mL in girls and 24.5 ng/mL in boys. It is particularly alarming that the vitamin D levels in children and adolescents decreases with increasing age. Boys aged 14–17 years and girls aged 11–13 years exhibit the lowest vitamin D levels, with 14.2 ng/mL and 13.7 ng/mL respectively. There were also clear seasonal differences in 25(OH)D levels. The lowest average levels were seen in February (→ 10.56 ng/mL) and the highest in August (→ 24.16 ng/mL). Children with a migration background had average levels clearly lower than those without such a background (13.4 ng/mL vs 16.7 ng/mL). Taking a cut-off of 20 ng/mL for the 25(OH)D level, 62% of the 3- to 17-year-old non-immigrants and 76% of the migrants had a vitamin D deficiency. Furthermore, as was to be expected, children and adolescents, who were overweight or obese, had clearly lower 25(OH)D levels than those of normal weight.

The results of the National Consumption Survey II showed that the daily vitamin D intake of > 96% of girls and 86% of boys aged 14–18 years failed to meet the recommendations [9, 10]. A recent European study, which collected data on the 25(OH)D status of 1006 adolescents aged between 12.5 and 17.5 years, showed that 39% of them had an inadequate vitamin D status (25(OH)D: 20-30 ng/mL), 27% a vitamin D deficiency, and 15% a severe vitamin D deficiency. In this study, only 19% had an adequate vitamin D status of 25(OH)D ≥ 30 ng/mL. To date, there are no studies on whether vitamin D supplements in children and adolescents can improve cerebral function to any extent. But we have to assume that children with a vitamin D deficiency [25(OH)D < 20 ng/mL] would benefit the most from targeted vitamin D supplementation with respect to their mental and physical development [8,9].

Recommendation

The results of these studies justify in any case the recommendation to improve the 25(OH)D status in children and adolescents through a healthy approach with exposure to sunlight, a good supply of vitamin-D-containing foodstuffs and vitamin D supplements. A good vitamin D intake should be ensured as a matter of principle for a healthy immunological, metabolic and neurological development. A healthy 25(OH)D status is characterised by 25(OH)D levels of 40-60 ng/mL or 100-150 nmol/L for all age groups. As it is not possible to provide an adequate supply of cholecalciferol via the diet and vitamin D can only be produced in Germany during the summer months with the help of sunlight, children and adolescents should be taking about 40-60 IU vitamin D per kg body weight daily in the form of vitamin D supplements.

Cerebral fatty acids: EPA and DHA

The long-chain polyunsaturated omega-3 fatty acids Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) are essential building blocks determining the function of every nerve cell membrane. For example, these fatty acids enhance the conduction of impulses at synapses in the Central Nervous System (CNS) by increasing neuronal membrane fluidity. In addition, EPA and DHA have an important role in nerve cell differentiation, intercellular communication, synaptogenesis, neurogenesis and gene expression. Lipid mediators derived from the long-chain omega-3 fatty acids, such as resolvins and protectins, have strong anti-inflammatory and neuroprotective actions. In all phases of life – but especially during pregnancy, childhood and adolescence – EPA and DHA are therefore of fundamental importance for the development of the brain and intelligence.

Fatty saltwater fish such as herrings, mackerel, salmon and cod are particularly rich in EPA and DHA. As the HELENA study shows, young people in Europe aged between 12.5 and 17.5 years do not eat enough fish, failing by far to meet the recommended daily intake. More than a third of the adolescents do not even consume the recommended quantity of Alpha-Linolenic Acid (ALA). The regular diet of many adolescents therefore carries a high risk of an insufficient supply of EPA and DHA. Various studies have reported an improvement in cognitive function (e.g. memory, attention) and scholastic performance (e.g. reading, spelling) in schoolchildren taking regular supplements of DHA and EPA [10,12].

Recommendation

When administering omega-3 fatty acids (e.g. omega-3 oil, algae oil), it is extremely important to ensure a regular intake of

EPA and DHA at a sufficiently high dose (~ 40-50 mg EPA/DHA per kg body weight per day). As a rule, it takes several months to see the first effects. With respect to cognitive function, children, who have a dietary deficiency of omega-3 fatty acids, may obtain the greatest benefit from EPA/DHA supplements (e.g. 3000 mg EPA/DHA per day). The HS-Omega-3 Index, which measures the concentrations of EPA and DHA in red blood cell membranes, can be used to assess the individual EPA and DHA status (target value: ≥ 10%).

Iron and intelligence

Besides its role in oxygen transport as a component of the haemoglobin molecule, iron plays an essential part in the synthesis of nucleic acids (DNA, RNA) and proteins, in cell growth and differentiation as well as in gene expression. In addition, iron is indispensable for the energy metabolism of neurones and glial cells as well as for the production of neurotransmitters (e.g. dopamine, serotonin), synaptogenesis and myelination. Worldwide, iron deficiency is by far the most common trace element deficiency. In Europe, the prevalence of iron deficiency is about 10% [10]. Iron deficiency may have a negative impact on cognitive function in children. Decreased motor activity, reduced social awareness and poorer scholastic performance have been observed in schoolchildren with anaemia. In general, iron deficiency can cause tiredness and impair performance even in the absence of anaemia. A good supply of iron and vitamins (e.g. vitamin D, vitamin A, vitamin C) in adolescents is also an important factor in physical performance (e.g. stamina, muscle strength), because iron is an integral component of the red blood cell pigment haemoglobin, which is responsible for carrying oxygen to the muscles, while antioxidants such as vitamin C promote regeneration after intensive training and vitamin D reinforces muscle strength via its interactions with vitamin D receptors.

There is an increased need for iron during growth phases, which cannot always be covered sufficiently through the diet. Therefore, an inadequate iron intake is often observed among adolescents. According to the results of the National Consumption Survey II, 58% of girls and 14% of boys in the 14–18 age group do not achieve the recommended daily intake of iron [13,14]. These results have also been confirmed by the recent HELENA study, which looked at the iron status of adolescents from 10 European countries. Serum ferritin levels (< 15 µg/L) were taken as the indicator of iron depletion, while soluble transferrin receptor (sTfR) levels (> 8.5 mg/L) together with iron depletion was taken as the indicator of iron deficiency. A serum ferritin level of < 15 µg/L is already evidence of depleted iron stores. A latent iron deficiency with non-haematological symptoms may already exist with ferritin levels of < 50 µg/L. As inflammatory processes can affect the quality of diagnostic investigations for iron, subjects with high C-reactive protein levels (CRP > 5 mg/L) were excluded from the analysis.

Data from 940 adolescents (502 girls, 438 boys) aged 12-17 years were analysed: iron depletion was found in 17.6% of the adolescents in Europe – with 21% in girls being significantly higher than 13.8% in boys ($p < 0.05$). Iron deficiency was demonstrated in 5.4% of the girls and 3.9% of the boys. Iron depletion in adolescents in Germany and Austria was found in 16% and 19% of those tested respectively. It is of note that the highest prevalence of iron depletion was found with 43% of girls in Ireland and 16% of boys in Denmark.

Recommendation

With respect to the cognitive function in children and adolescents, an adequate intake of iron-containing foods (e.g. meat, fish, poultry) should be ensured as a matter of principle in accordance with the FKE concept of an optimally balanced diet. Following a medical check-up with laboratory testing (e.g. ferritin, CRP, liver function tests, soluble transferrin receptors), regular iron supplements in an easily bioavailable form can be recommended for those in risk groups, such as girls with a higher iron requirement due to the onset of menstrual bleeding or young people, who are vegetarians.

B Vitamins and a healthy nervous system

The B vitamins work closely together supporting various bodily functions. Vitamin B_1, vitamin B_2 and vitamin B_{12} are important for mitochondrial energy metabolism, acting in the production of cell energy in the form of ATP. Folic acid and vitamin B_{12} are involved mainly in the processes of cell division and new cell formation (e.g. blood cells, mucosa). Together with vitamins B_2 and B_6, folic acid and B_{12} are absolutely essential for the normal functioning of the nervous system and cognitive function. The synthesis of neurotransmitters (e.g. serotonin, dopamine) and the integrity of the myelin sheath surrounding nerve fibres depend on an adequate supply of these B vitamins.

According to the results of the National Consumption Survey II, 78% of the girls and 66% of the boys aged between 14 and 18 years do not achieve the recommended daily intake of folic acid (400 µg dietary folate). The average daily intake of dietary folate in young women is only 252 µg. 8% of young men and 33% of young women aged 14-24 years do not achieve the recommended daily intake of vitamin B_{12} [15]. A recent multicentre study on 1051 European adolescents (age: 12.5-17.5 years) recorded the dietary intake of B vitamins on the basis of the folic acid, vitamin B_6 and vitamin B_{12} levels in the blood as well as the plasma homocysteine concentrations. The average vitamin B_{12} level in serum was 319 pmol/L (= 432 pg/mL). 5% had an inadequate intake of vitamin B_{12} based on the holotranscobalamin levels (an early marker of B_{12} deficiency), 10% had an inadequate intake of folic acid based on the red blood cell folic acid concentration and 20% had an inadequate intake of vitamin B_6 as shown by the pyridoxal 5-phosphate concentrations. 5% of the adolescents studied had raised plasma homocysteine levels. This shows that there is risk of folic acid, vitamin B_6 and B_{12} deficiencies with pathological levels due to the poor nutrition provided by the regular diet of a considerable number of people.

The serum vitamin B_{12} concentration is a later, relatively insensitive and non-specific biomarker of B_{12} deficiency. A functional vitamin B_{12} deficiency cannot be ruled out even with values of < 450 pg/mL. With serum B_{12} levels of < 450 pg/mL, non-specific neurological symptoms of B_{12} deficiency may already occur. In contrast, holotranscobalamin (holoTC), also called known as active B_{12}, is the earliest laboratory parameter to reveal B_{12} deficiency [16]. In older people, raised homocysteine levels induced by vitamin B_{12} deficiency are a significant risk factor for neurodegenerative diseases (e.g. dementia) and correlate strongly with atrophy in the frontal, parietal and occipital regions of the brain. Lowering these elevated homocysteine levels by the administration of B vitamins reduces the incidence of cerebral atrophy in patients with mild cognitive impairment.

Plasma homocysteine levels are inversely proportional to the folic acid levels in the blood. The reason for this is the inadequate provision of methyl groups through 5-methyltetrahydrofolate (5-MTHF) in the case of folic acid deficiency; these methyl groups are required for the remethylation of homocysteine to L-methionine. Gene polymorphism of 5-MTHF reductase is often a contributary factor here. Studies on adolescents show an inverse correlation of the body weight and Body Mass Index (BMI) with the folic acid and vitamin B_{12} status. One study on 60 children and adolescents aged 7 to 17 years found significantly higher homocysteine levels in the overweight subjects than in those of normal weight (14.3 ± 11.8 µmol/L vs 8.7 ± 5.9 µmol/L, p=0.017) [17]. In short-term interventional studies on preschool children, folic acid, vitamin B_2, B_6 and B_{12} supplements lowered the plasma homocysteine levels and improved folic acid balance. On the other hand, there was no improvement in the cognitive function of these children.

Recommendation

With respect to cognitive function in adolescents, an adequate intake of folic-acid-containing foods (e.g. vegetables, fruit, pulses) should be ensured as a matter of principle in accordance with the FKE concept of an optimally balanced diet. Additional folic acid, vitamin B6 and B12 supplements in physiological doses are to be recommended in risk groups, such as girls regularly taking oral contraceptives. Children brought up on a vegan diet cannot obtain an adequate supply of vitamin B12 unless they are given nutritional supplements.

Antioxidants: vitamin C, vitamin E & co

Especially during childhood and adolescence, an adequate nutritional status of antioxidant vitamins (e.g. vitamin C, E) and carotenoids is essential because of its importance for cell growth and cell development. In addition, various neuroprotective effects have been ascribed to vitamin E. According to the results of the National Consumption Survey II, 29% of the girls and 32% of the boys aged between 14 and 18 years do not achieve the recommended daily vitamin C intake of 100 mg. In addition, 48% of young men and 49% of young women aged 14–24 years do not achieve the recommended daily intake of 15 mg vitamin E. A recent multicentre study on 1054 European adolescents (age: 12.5-17.5 years) recorded the dietary intake of antioxidant vitamins on the basis of the vitamin C, vitamin E, vitamin A and beta-carotene levels in the blood. The average vitamin E concentration was 23 µmol/L and the vitamin C concentration 59 µmol/L. From the point of view of prevention, the intake of these antioxidant vitamins can be considered suboptimal. In the prevention of cardiovascular disease and cancer, every effort should be made to achieve vitamin C levels of ≥ 70 µmol/L and vitamin E levels of > 30 µmol/L. The regular consumption of antioxidant-rich fruit and vegetables should easily provide these preventative plasma concentrations. In addition, epidemiological studies and prospective case-control studies have yielded evidence that eating more fruit and vegetables reduces the risk of cognitive impairment [18,19].

Recommendation

The FKE concept of an optimally balanced diet basically considers that adolescents should, as a matter of principle, have an adequate intake of antioxidant-rich foods (e.g. fresh fruit, vegetables). They should eat at least 300 g fresh fruit and 300 g fresh vegetables daily.

Multivitamins and scholastic performance – A selection.

Various studies on children and adolescents have achieved an improvement in cognitive function (e.g. attention, memory, concentration, nonverbal intelligence, verbal learning) with the regular administration of multivitamin/mineral supplements (**Table 2**).

With respect to scholastic performance, children and adolescents with unhealthy eating habits will particularly benefit from nutritional supplements. But it is only worthwhile, if these products are taken regularly and consistently for several weeks.

Table 2: Effects of multivitamin preparations on cognitive function in children and adolescents – A selection [20-25].

Age (± years)	Number	Intervention (per day)	Duration	Cognitive effects
14 years	615	5000 IU Vitamin A (VA), 1.5 mg VB1, 1.7 mg VB2, 20 mg VB3, 10 mg VB5, 2 mg VB6, 300 µg biotin, 400 µg folic acid, 6 µg VB12, 60 mg VC, 400 IU VD, 30 IU VE, 50 µg VK, 200 mg Ca, 2 mg Cu, 0.10 mg Cr, 18 mg Fe, 150 µg I, 80 mg Mg, 2.5 mg Mn, 0.25 mg Mo, 100 µg Se, 15 mg Zn	13 weeks	Positive effects of micronutrient supplements (100% according to RDA) on nonverbal intelligence (p=0.01)
9.5 years	30	375 µg VA, 3.9 mg VB1, 5 mg VB2, 50 mg VB3, 50 mg VB5, 12 mg VB6, 100 µg biotin, 100 µg folic acid, 10 µg VB12, 500 mg VC, 3 µg VD, 70 IU VE, 100 µg VK; 100 mg Ca, 0.2 mg Cr, 1.3 mg Fe, 50 µg I, 7.6 mg Mg, 1.5 mg Mn, 0.1 mg Mo, 10 mg Zn, 50 mg Bioflavo, 70 mg choline bitartrate, 30 mg inositol, 10 mg PABA	13 weeks	Positive effects of micronutrient supplements on nonverbal intelligence (p = 0.02)
8.9	468	750 µg VA, 0.75 mg VB1, 0.85 mg VB2, 10 mg VB3, 5 mg VB5, 1 mg VB6, 200 µg folic acid, 3 µg VB12, 40 mg VC, 20 mg VE, 5 µg VD, 50 µg Cr, 1 µg Cu, 9 mg Fe, 1.25 µg Mn, 0.12 µg Mo, 50 µg Se, 7.5 mg Zn	13 weeks	Positive effects of micronutrient supplements on nonverbal intelligence (2.5 IQ points; 95% CI: 1.85, 2.15)
8.7	396	400 µg VA, 1 mg VB6, 150 µg folic acid, 1.5 µg VB12, 45 mg VC, 10 mg Fe, 5 mg Zn	52 weeks	Positive effects of micronutrient supplements on verbal learning and memory (effect strength 0.23, 95% CI; 0.01, 0.46)
9.2	569	270 µg VA, 5 mg Fe, 50 µg I, 5 mg Zn	31 weeks	Positive effects of micronutrient supplements on visual memory (0.5 points more; 95% CI; 0.1, 0.9)
13	167	5000 IU VA, 1.5 mg VB1, 1.7 mg VB2, 20 mg VB3, 2 mg VB6, 400 µg folic acid, 6 µg VB12, 60 mg VC, 400 IU VD, 15 IU VE, 1.6 mg Ca, 2 mg Cu, 18 mg Fe, 25 mg Mg, 1 mg Mn, 10 mg Zn	22 weeks	Positive effects of micronutrient supplements on non-verbal intelligence in adolescents with an unhealthy diet (< 50% der RDA) (p < 0.02)

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