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Influences of micronutrient and omega-3 fatty acid supplementation on cognition, learning, and behavior: methodological considerations and implications for children and adolescents in developed societies

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The purpose of this review is to outline the current evidence regarding the effects of micronutrient and omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation on the cognition, learning, and behavior of children and adolescents living in developed societies. Existing evidence suggests that children and adolescents in developed countries may perform better on tests of nonverbal intelligence and on behavioral measures after receiving vitamin and mineral supplements with or without n-3 PUFA supplementation compared with those receiving placebo, regardless of age and supplementation formula. The strongest effects were observed in trials that lasted over 3 months and in subgroups of children with low socioeconomic status, symptoms of attention deficit hyperactivity disorder, and/or learning disabilities. Future studies should focus on children and adolescents who have a low socioeconomic status or are likely to be suffering nutritional deficiencies to determine the impact of vitamin and mineral supplements with or without n-3 PUFA supplementation on their cognitive and behavioral functioning. These studies should ideally include blood sample analyses to help determine if nutritional status influences the response to supplementation and whether changes in blood status account for effects on cognition and behavior.

INTRODUCTION

In developed countries such as Australia, children from all socioeconomic strata are at risk of suffering from nutritional deficiencies. Results from the most recent Australian National Children's Nutrition and Physical Activity Survey[1] indicate that, typical of a contemporary Western dietary pattern, Australian children have an intake of fruit and vegetables that is well below dietary guidelines, and they are consuming excessive amounts of noncore foods (i.e., foods that do not fit into the Australian Guide to Healthy Eating's five core food groups). An analysis of this survey[2] shows, as do other recent studies,[3] that Australian children and adolescents have very low intake of omega-3 polyunsaturated fatty acids (n-3 PUFAs). This low intake is concerning, not only for the physical, but also for the cognitive development of Australian youth, as this may put them at increased risk for learning and behavioral problems, given that these nutrients are essential for brain function.[4,5]

Nutrition has been thought to play a key role in the cognitive functioning, learning, and behavior of children, but it is critical during adolescence, when the body undergoes a significant period of growth, particularly regarding brain development. For the purpose of this review, adolescence is considered as the period between the age of

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about 12 years through the early twenties, as the entire second decade is often referred to as adolescence,[6] and even ages up to 25 years have been considered late adolescence.[7,8] The prefrontal cortex of the brain undergoes considerable maturation during childhood and adolescence, involving a reduction of neuronal and synaptic density, growth of dendrites, and an increase in white matter volume.[9–11] The prefrontal cortex is thought to be the brain area that gives rise to the executive functions that include planning, attention, strategic thinking, social cognition, emotional regulation, and impulse control.[12–16] Importantly, there is a link between the proper development of these abilities and social, emotional, and motivational functions that influence learning and behavior,[17,18] due to strong connections between the prefrontal cortex and the limbic system.[18] Optimal nutrition is important for healthy brain development and function.[19–22] Accordingly, the results of prospective longitudinal studies have suggested that poor nutrition impacts not only children's physical health but also cognition, behavior, and neurodevelopmental outcomes.[5,23,24] Given this intricate interplay between nutrients and brain function, a number of randomized clinical trials have investigated the effects of supplementation with vitamins and minerals (micronutrients) and/or essential fatty acids on intelligence, academic performance, cognitive ability, and behavioral outcomes in children and adolescents. Table 1 and Table 2 provide overviews of studies investigating the effects of micronutrient supplementation (Table 1) or n-3 PUFA supplementation (Table 2) on cognition, learning, and behavior in children and adolescents in developed countries, while Table 3 provides an overview of studies investigating the effects of combined micronutrient and n-3 PUFA supplementation on behavior in young adults in correctional facilities, including a calculation of effect sizes for the findings where possible. These will be reviewed here.

Effect of micronutrient supplementation on cognition, learning, and behavior

A number of studies have investigated the impact of vitamin and mineral supplementation on cognitive, learning, and behavioral outcomes, many with a focus on performance on intelligence tests. While a few studies found no significant differences between placebo and supplementation groups, the majority of the literature suggests a positive effect of supplementation on intelligence-test scores. These studies and the methodological considerations that may contribute to positive versus negative outcomes will be discussed.

Most of the studies reporting significant changes in intelligence measured nonverbal (fluid) rather than verbal (crystallized) intelligence. In 1988, a study conducted in Wales reported a significant increase in the performance of 90 schoolchildren in nonverbal intelligence after 35 weeks of vitamin and mineral supplementation,[25] with a 7.2-point greater gain in nonverbal intelligence than the placebo group and a 5.0-point greater gain than the no-treatment group on a 100-point scale. One limitation of this study was a lack of assessment of the children for their blindness to treatment and the absence of multiple measures of IQ (only one verbal test and one nonverbal test were used).

Several attempts to replicate these findings have been reported, some producing nonsignificant results. In 1990, a study conducted among 227 British schoolchildren found no improvement on intelligence-test scores following 28 days of vitamin and mineral supplementation compared with placebo.[26] Prior to randomization, the older children and the parents of the younger children weighed and recorded food and drink consumed for 7 consecutive days with digital scales. There were no consistent correlations between test scores and micronutrient intakes, based on the weighed records. Among 7–10-year-olds, there were no significant differences in performance between supplemented and placebo groups in nonverbal test scores (effect size $d = 0.39$), digit span scores ($d = 0.11$), or coding scores ($d = {}^{-}0.09$). There were also no significant differences in 11–12-year-olds between the supplement and placebo groups in nonverbal test scores ($d = 0.01$), digit span scores ($d = 0.05$), or coding scores ($d = 0.18$), and overall, effect sizes were low. This study was not a true replication of the previous study due to the significantly shorter supplementation period (1 month as opposed to 8 months), use of different intelligence tests, retests being performed after a much shorter period, and the use of a different supplementation formula, making it difficult to compare results. The reliability of the results is somewhat questionable, as the parents and children weighed and recorded the food and drink consumption themselves. There has been criticism of the tests used in this study, specifically that the Alice Heim test (AH1) is a group-administered test, which may influence its validity, and that it may be more reflective of perceptual reasoning rather than nonverbal intelligence, as assumed by the researchers.[27] Carroll[27] also was concerned that the Wechsler Intelligence Scale for Children Revised (WISC-R) was not used in a valid manner, as only one of the five nonverbal scales was used to measure nonverbal IQ, and only one verbal scale was used to measure verbal IQ. The WISC-R manual states that, in order to produce a valid measure of nonverbal and verbal IQ, the participant must be tested on at least four of the five subscales. Therefore, as the combination of tests used in this study do not together provide a valid and reliable measure of intelligence (as it is defined by these tests), the authors may not be justified in making conclusions

Table 1 **Studies on the effects of micronutrient supplementation on cognition, learning, and behavior in children and adolescents in developed countries, with effect sizes calculated (small effect = 0.2; medium effect = 0.5; large effect = 0.8).**

Reference	Study design	Participants	Intervention (daily dosage)	Trial length	Variables measured	Findings
No effect						
Nelson et al. (1990)[26]	Double-blind, placebo-controlled trial	$n = 227$, 7–12-year-old children in England	Vitamins: 1,000 µg vitamin A, 2.2 mg thiamine, 2.8 mg riboflavin, 24 mg vitamin B_3, 50 mg vitamin B_5, 2 mg vitamin B_6, 100 µg biotin, 450 µg folate, 5 µg vitamin B_{12}, 50 mg vitamin C, 10 mg vitamin E, 15 µg vitamin D, 100 µg vitamin K Minerals: 100 mg Ca, 200 µg Cr, 2 mg Cu, 15 mg Fe, 100 µg I, 25 mg Mg, 1.5 mg Mn, 150 µg Se, 15 mg Zn Placebo tablets	4 weeks	AH1X test of nonverbal intelligence, AH4 parts I and II, WISC-R Digit Span and Coding tests	No significant differences in performance between the supplement and placebo groups in nonverbal test scores in 7–10-year-olds ($d = 0.39$), Digit Span scores ($d = 0.11$), or Coding scores ($d = -0.09$). No significant differences in 11–12-year-olds in verbal test scores ($d = 0.01$), nonverbal test scores ($d = -0.07$), Digit Span scores ($d = 0.05$), or Coding scores ($d = 0.18$).
Crombie et al. (1990)[28]	Randomized, placebo-controlled trial	$n = 86$, 11–13-year-old schoolchildren in Scotland	Vitamins: 375 µg vitamin A, 3.9 mg thiamine, 5 mg riboflavin, 50 mg vitamin B_3, 50 mg vitamin B_5, 12 mg vitamin B_6, 100 µg biotin, 100 µg folate, 10 µg vitamin B_{12}, 500 mg vitamin C, 3 µg vitamin D, 70 IU vitamin E, 100 µg vitamin K Minerals: 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 Other: 50 mg bioflavanoids, 70 mg choline bitartrate, 30 mg inositol, 10 mg PABA Placebo tablets	30 weeks	Calvert Non-Verbal Test, the Verbal Battery of the CAT, Cattell Culture-Fair, Raven's Standard Progressive Matrices, AH4 parts I and II	No significant differences in performance between the supplement and placebo groups. Effect sizes could not be calculated.
Naismith et al. (1988)[30]	Double-blind, placebo-controlled trial	$n = 154$, 11–12-year-old schoolchildren in England	Vitamins: 375 µg vitamin A, 3.9 mg thiamine, 5 mg riboflavin, 50 mg vitamin B_3, 50 mg vitamin B_5, 12 mg vitamin B_6, 100 µg biotin, 100 µg folate, 10 µg vitamin B_{12}, 500 mg vitamin C, 3 µg vitamin D, 70 IU vitamin E, 100 µg vitamin K Minerals: 100 mg Ca, 2 mg Cu, 0.2 mg Cr, 1.3 mg Fe, 50 µg I, 7.6 mg Mg, 1.5 mg Mn, 0.1 mg Mo, 150 µg Se, 10 mg Zn Other: 50 mg bioflavanoids, 70 mg choline bitartrate, 30 mg inositol, 10 mg PABA Placebo tablets	4 weeks	AH4 parts I and II, WISC-R	Scores on the intelligence retests were higher than the original scores in both groups. There were no significant differences in performance between the supplement and placebo groups in verbal test scores ($d = 0.01$), nonverbal test scores ($d = 0.04$), Digit Span scores ($d = 0.17$), and Coding scores ($d = 0.01$).
Perlman et al. (2010)[41]	Double-blind, placebo-controlled clinical trial	$n = 684$, 8–12-year-old schoolchildren in the USA	Standard children's multivitamin/mineral tablet, which provided 100% of the RDA established by the US FDA for ages 4–12 years for most vitamins and minerals, with the exception of Ca, Mg, Cu, and Fe, for which values were 12.5%, 18%, 50%, and 50% of the recommended daily values, respectively Placebo tablets	39 weeks	TerraNova, grade point average, attendance, tardiness, incidents of misbehavior	No significant improvement for TerraNova national percentile total scores ($d = 0.05$), number of days absent from school ($d = 0.03$), tardiness ($d = 0.04$), or grade point average in reading ($d = 0$), language ($d = -0.12$), mathematics ($d = -0.10$), science ($d = -0.12$), and social science ($d = 0$) between the supplement and placebo groups.
Positive effects or outcomes						
Benton & Roberts (1988)[25]	Double-blind, placebo-controlled trial	$n = 90$, 12–13-year-old schoolchildren	Vitamins: 375 µg vitamin A, 3.9 mg thiamine, 5 mg riboflavin, 50 mg vitamin B_3, 50 mg vitamin B_5, 12 mg vitamin B_6, 100 µg biotin, 100 µg folate, 10 µg vitamin B_{12}, 500 mg vitamin C, 3 µg vitamin D, 70 IU vitamin E, 100 µg vitamin K Minerals: 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 Other: 50 mg bioflavanoids, 70 mg choline bitartrate, 30 mg inositol, 10 mg PABA Placebo tablets No treatment	35 weeks	Verbal battery of the CAT, Calvert Non-Verbal Test	Supplement group gained 7.2 points more in nonverbal intelligence than the placebo group and 5.0 points more than the no treatment group, with the differences being statistically significant ($P < 0.01$). Effect sizes could not be calculated.

Benton & Buts (1990)[35]	Double-blind, placebo-controlled trial	$n = 167$, 13-year-old schoolchildren in Belgium	Vitamins: 5,000 IU vitamin A, 1.5 mg thiamine, 1.7 mg riboflavin, 20 mg vitamin B_3, 2 mg vitamin B_6, 400 µg folate, 6 µg vitamin B_{12}, 60 mg vitamin C, 400 IU vitamin D, 15 IU vitamin E Minerals: 1.6 mg Ca, 2 mg Cu, 18 mg Fe, 25 mg Mg, 1 mg Mn, 10 mg Zn Placebo tablets	22 weeks	Flemish-speaking children took the Calvert Non-Verbal Test and the Differentiele Geschiktheidsbatteri, French- speaking children took the Les Examens Otis-Oiiawa d'H abileté Mentale	Positive effect of supplementation on nonverbal IQ in boys with diet low in micronutrients (≈<50% RDA), $P < 0.02$. Effect sizes could not be calculated.
Benton & Cook (1991)[31]	Double-blind, placebo-controlled trial	$n = 47$, 6-year-old children	Vitamins: 300 µg vitamin A, 0.7 mg thiamine, 0.9 mg riboflavin, 10 mg vitamin B_3, 25 mg vitamin B_5, 1.3 mg vitamin B_6, 10 µg biotin, 200 µg folate, 2.5 µg vitamin B_{12}, 70 mg vitamin C, 6 mg vitamin E, 10 µg vitamin D, 100 µg vitamin K Minerals: 30 mg Ca, 30 µg Cu, 100 µg Cr, 2.4 mg Fe, 50 µg I, 8 mg Mg, 1 mg Mn, 0.1 mg Mo, 4 mg Zn Other: 20 mg bioflavonoids, 35 mg choline bitartrate, 15 mg inositol, 5 mg PABA Placebo tablets	6 weeks in one school, 8 weeks in another school	Four subtests of the British Ability Scale (recall of digits, matrices, similarities, and naming vocabulary)	The IQ of children taking the supplement increased by 7.6 points, whereas the placebo was associated with a decline of 1.7 points ($d = 0.63$). The supplement group showed improved performance compared with the placebo group in both the nonverbal measures of the British Ability Scale, recall of digits ($d = 0.89$), and matrices ($d = 0.59$). The verbal measures were calculated for each of the two schools: the supplement groups in both schools 1 and 2 showed increased performance in verbal similarities ($d = 1.03$ and $d = 0.39$, respectively). In naming vocabulary, school 1 showed improved performance ($d = 0.82$), while school 2 showed declined performance ($d = -0.09$). Those in the supplement group were significantly more likely to concentrate ($P < 0.027$) and less likely to fidget ($P < 0.043$) during a frustrating television task compared with the placebo group.
Schoenthaler et al. (1991)[33]	Double-blind, placebo-controlled trial	$n = 26$, 13–16-year-old juveniles	Vitamins: 5,000 IU vitamin A, 120 mg vitamin C, 4.5 mg thiamine, 5.1 mg riboflavin, 60 mg niacin, 6 mg pyridoxine, 30 mg pantothenic acid, 400 µg folic acid, 18 µg cyanocobalamin, 200 IU vitamin D, 30 IU vitamin E, 300 µg biotin, 30 mg pyridoxal 5-phosphate Minerals: 122 mg Ca, 2 mg Cu, 18 mg Fe, 59 mg Mg, 5 mg Mn, 18 mg P, 15 mg Zn Other: 40 mg choline, 40 mg inositol, 50 mg PABA	13 weeks	WISC-R, blood nutrients	The supplement group produced significantly larger gains in nonverbal IQ (+6 points) than the placebo group (–1 point) ($d = 0.48$). Participants with improved blood nutrient concentrations after supplementation showed a significantly greater increase in nonverbal IQ scores (+11.6 points) compared with those whose blood concentrations remained unchanged (–2.7 points) ($d = 1.01$).
Schoenthaler et al. (1991)[32]	Triple-blind, placebo-controlled trial	$n = 410$, 12–16-year-old schoolchildren in the USA	One of three different strength vitamin-mineral supplements (50%, 100%, or 200% US RDA) The 100% supplement contained the following: Vitamins: 5,000 IU vitamin A, 1.5 mg thiamine, 1.7 mg riboflavin 20 mg vitamin B_3, 10 mg vitamin B_5, 2 mg vitamin B_6, 300 µg biotin, 400 µg folate, 6 µg vitamin B_{12}, 60 mg vitamin C, 400 IU vitamin D, 30 IU vitamin E, 50 µg vitamin K. Minerals: 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, 0.10 mg Se, 15 mg Zn Placebo tablets	12 weeks	WISC-R, MAT, RT/IT, CTBS, Raven's Matrices, EPQ, blood samples	Significant improvements in nonverbal IQ on the WISC-R (difference of 3.7 gain between the placebo group and the 100% supplement group, $d = 0.49$).
Schoenthaler et al. (1997)[34]	Double-blind, placebo-controlled trial	$n = 62$, 13–17-year-old delinquents	12 vitamins and 11 minerals set at approx. 100% US RDA for minerals and 300% US RDA for most vitamins. The amounts of Ca (122 mg), Mg (59 mg), and vitamin D (200 IU) were lower. Only the amounts of vitamin C (120 mg) and pyridoxine (30 mg) were higher than 300%. Vitamin A and folate were set at the US RDA. Other: 40 mg choline, 40 mg inositol, 50 mg PABA Placebo tablets	13 weeks	7-day dietary survey, blood samples, violent rule infractions, nonviolent rule infractions, total rule infractions	A significant difference between supplement and placebo groups was found for violent and nonviolent antisocial behavior, with a net difference of 28%. Among 10 subjects who maintained their normal or low blood vitamin concentrations throughout the trial, there was no marked change in violence. The 16 subjects in whom low blood vitamin concentrations were corrected committed 131 violent acts during baseline and 11 during intervention.

Table 1 **Continued**

Reference	Study design	Participants	Intervention (daily dosage)	Trial length	Variables measured	Findings
Snowden (1997)[36]	Triple-blind, placebo-controlled trial	*n* = 30, 9–10-year-old children in England	Vitamins: 375 μg vitamin A, 3.9 mg thiamine, 5 mg riboflavin, 50 mg vitamin B_3, 50 mg vitamin B_5, 12 mg vitamin B_6, 100 μg biotin, 100 μg folate, 10 μg vitamin B_{12}, 500 mg vitamin C, 3 μg vitamin D, 70 IU vitamin E, 100 μg vitamin K Minerals: 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 Other: 50 mg bioflavanoids, 70 mg choline bitartrate, 30 mg inositol, 10 mg PABA Placebo tablets	10 weeks	Verbal Battery of the CAT, Calvert Non-Verbal Test	A significant difference in gains in nonverbal IQ between supplement and placebo groups ($P = 0.0208$) over the placebo group. Effect sizes could not be calculated.
Schoenthaler et al. (2000)[29]	Double-blind, placebo-controlled trial	*n* = 245, 6–12-year-old schoolchildren in the USA	Vitamins: 750 μg vitamin A, 0.75 mg thiamine, 0.85 mg riboflavin, 10 mg vitamin B_3, 5 mg vitamin B_5, 1 mg vitamin B_6, 200 μg folate, 3 μg vitamin B_2, 40 mg vitamin C, 20 mg vitamin E, 5 μg vitamin D Minerals: 50 μg Cr, 1 μg Cu, 9 mg Fe, 1.25 μg Mn, 0.12 μg Mo, 50 μg Se, 7.5 mg Zn Placebo tablets	13 weeks	WISC-R	A significant difference of 2.5 IQ points was found between the supplement and placebo groups ($d = 0.17$, $P = 0.038$). A significantly higher proportion of children in the supplement group gained 15 or more IQ points when compared with the placebo group ($P < 0.01$).
Carlton et al. (2000)[39]	Double-blind, placebo-controlled trial	*n* = 20, children with learning disabilities (7–14 years)	Vitamins: 50 mg thiamine, 50 mg vitamin B_3, 25 mg vitamin B_5, 100 mg vitamin B_6, 500 μg vitamin B_{12}, 400 μg folic acid, 100 mg vitamin C Minerals: 100 mg Mg, 20 mg Mn, 22.5 mg Zn Other: 500 mg L-tyrosine, 500 mg L-glutamine, 500 mg linolenic acid, 10 mg coenzyme Q10 Placebo tablets	4 years (year 1 = open-label trial, year 2 = closed trial, year 3 = first-year follow-up, year 4 = second-year follow up)	WISC; WRAT, Detroit Test of Learning Aptitude, Test of Written Language, Woodcock Reading Mastery, Coopersmith Self-Esteem Inventory, the Stanford Achievement Test, Bender-Gestalt	No significant differences in any of the IQ measures, but there were significant improvements in academic and behavioral outcomes within a few weeks or months of open-label treatment. Twelve children completed the 1-year double-blind phase, after which almost half of the children chose to remain on the nutrients for an additional 2 years. It took at least 1 year to see the first indications of a decline in academic performance, while for children who remained on nutrients, the gains continued the upward trend; at the end of year 4, the difference in scores between the two groups reached statistical significance ($P < 0.01$, $d = 1.88$).
Osendarp et al. (2007)[40]	Double-blind, randomized controlled trial	*n* = 396, 6–10-year-old children in Australia	Micronutrient mix: Vitamins: 400 μg RE vitamin A, 1 mg vitamin B_6, 150 μg folate, 1.5 μg vitamin B_{12}, 45 mg vitamin C Minerals: 10 mg Fe, 5 mg Zn DHA + EPA mix: 88 mg DHA, 22 mg EPA Micronutrients + DHA + EPA Placebo drink	52 weeks	WISC-III, NEPSY, WAIS-III, RAVLT, WIAT Screener	Significant positive effect of supplementation on verbal learning and memory factor in the supplement group compared with the placebo group ($d = 0.23$). No significant effects were observed on the other factors (general intelligence and visual attention). There were no significant interactions between micronutrients and DHA and EPA for change in factor scores.

Abbreviations: AH1, AH4, Alice Heim tests; Ca, calcium; CAT, Cognitive Abilities Test; CTBS, Comprehensive Test of Basic Skills; Cu, copper; *d*, Cohen's d; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPQ, Eysenck Personality Questionnaire; FDA, Food and Drug Administration; Fe, iron; I, iodine; IU, international units; MAT, Miller Analogies Test; Mg, magnesium; Mn, manganese; Mo, molybdenum; NEPSY, Developmental Neuropsychological Assessment; PABA, para-aminobenzoic acid; RAVLT, Rey Auditory Verbal Learning Test; RDA, recommended daily allowance; RT/IT, reaction time and inspection time; Se, selenium; WAIS-III, Wechsler Adult Intelligence Scale – Third Edition; WIAT Screener, Wechsler Individual Achievement Test; WISC-III, Wechsler Intelligence Scale for Children – Third Edition; WISC-R, Wechsler Intelligence Scale for Children – Revised; WRAT, Wide Range Achievement Test; Zn, zinc.

Table 2 **Studies on the effects of omega-3 fatty acid supplementation on cognition, learning, and behavior in children and adolescents in developed countries, with effect sizes calculated (small effect = 0.2; medium effect = 0.5; large effect = 0.8).**

Reference	Study design	Participants	Intervention (daily dosage)	Trial length	Variables measured	Findings
Healthy sample						
McNamara et al. (2010)[74]	Double-blind, placebo-controlled trial	$n = 33$, 8–10-year-old healthy boys	400 mg DHA 1,200 mg DHA Placebo tablets	8 weeks	CPT-IP, fMRI scans	Significantly improved sustained attention and corresponding brain activation in those who received low-dose (by 47%) or high-dose (by 70%) DHA supplementation, but not in those who received placebo (–11%).
ADHD and developmental disorders						
Stevens et al. (2003)[68]	Double-blind, placebo-controlled trial	$n = 50$, 6–12-year-old children with ADHD from Indiana, USA	480 mg DHA, 80 mg EPA, 40 mg AA, 96 mg GLA, 24 mg vitamin E Placebo tablets	17 weeks	ASQ, DBD Rating Scale, CPT, eight tests of cognitive ability using the WJ-R	PUFA supplementation resulted in a substantial increase in the proportions of EPA, DHA, and α-tocopherol in plasma phospholipids and erythrocyte total lipids. Significant improvements in conduct problems rated by parents (–42.7 vs. –9.9%, $P = 0.05$) and in attention symptoms rated by teachers (–14.8 vs. +3.4%, $P = 0.03$). PUFA supplementation led to a greater number of participants showing improvement in oppositional defiant behavior from a clinical to a nonclinical range compared with placebo (8 of 12 vs. 3 of 11, $P = 0.02$). Effect sizes could not be calculated.
Richardson & Montgomery (2005)[63]	Double-blind, placebo-controlled trial	$n = 117$, 5–12-year-old children with developmental coordination disorder	60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg vitamin E Placebo tablets	26 weeks (one-way crossover after 3 months)	MABC, WORD, CTRS	Significant improvements in the supplement group compared with placebo in reading ($d = 0.41$, $P < 0.04$), spelling ($d = 0.34$, $P < 0.001$), and CTRS-L scores ($d = –0.61$, $P < 0.0001$) over 3 months of treatment in parallel groups. After a one-way crossover, similar changes were seen in the placebo-to-supplement group, while children continuing with the supplement maintained or improved their progress.
Sinn & Bryan (2007),[48] Sinn et al. (2008)[49]	Double-blind, placebo-controlled trial	$n = 132$ (questionnaire available for 104), 7–12-year-old children with ADHD from South Australia	60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg vitamin E Placebo tablets	30 weeks (one-way crossover after 15 weeks)	CPRS, CTRS, vocabulary subtests from the WISC-III, TEA-ch, Stroop	After 15 weeks, there were strong improvements in children's ability to control attention ($d = 0.43$) and switch attention ($d = 0.37$) in the PUFA groups compared with placebo. There were also improvements in vocabulary ($d = 0.31$). There were no effects on teacher ratings. Also after 15 weeks, there were significant improvements in the PUFA treatment groups compared with placebo groups in several CPRS scores, including cognitive problems/inattention ($d = 0.52$), ADHD Index ($d = 0.59$), CGI Restless/Impulsive ($d = 0.45$), both DSM-IV symptoms subscales Inattentive ($d = 0.61$) and Hyperactive/Impulsive ($d = 0.20$), and oppositional behavior ($d = 0.43$). During phase 2 (weeks 16–30), when all groups switched to active treatment, the placebo group showed significant improvements on CPRS comparable with the PUFA groups, with the exception of oppositional behavior. The placebo group also showed improvement in the ability to switch and control attention. The PUFA groups showed continued improvement in attention control and significant improvements in vocabulary. They also continued to show significant improvements in CPRS core symptoms.
Johnson et al. (2009)[62]	Double-blind, placebo-controlled trial	$n = 75$, 8–18-year-old children and adolescents with ADHD from Sweden	60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg vitamin E Placebo tablets	26 weeks (one-way crossover after 3 months)	ADHD-RS-IV, CGI	A greater reduction of symptoms in the supplement group compared with placebo in ADHD-RS-IV total scores ($d = –0.36$), inattention ($d = –0.31$), and hyperactivity/impulsivity ($d = –0.29$), but these differences were not significant. Baseline CGI scores decreased significantly in the supplement group compared with the placebo group ($d = –0.64$). A subgroup of 26% responded with more than a 25% reduction of ADHD symptoms and had a drop in CGI scores from moderate/marked severity to near normal at 3 months compared with placebo. This subgroup is described as having ADHD inattentive subtype and comorbid neurodevelopmental disorders.

Table 2 **Continued**

Reference	Study design	Participants	Intervention (daily dosage)	Trial length	Variables measured	Findings
Milte et al. (2012)[69]	Double-blind, placebo-controlled trial	$n = 54$ (45 with blood samples), 7–12-year-old children with ADHD or ADHD symptoms (50% diagnosed)	1,109 mg EPA and 108 mg DHA 103 mg DHA and 264 mg EPA Placebo tablets	52 weeks (3 × 3 crossover)	CPRS, word reading and spelling subtests from the WIAT-III; vocabulary subtest from the WISC-III; TEA-ch	Increased erythrocyte DHA was associated with improved word reading ($r = 0.394$) and reduced parental ratings of oppositional behavior ($r = 0.392$) in the whole sample. These effects were much stronger in a subgroup of 17 children with learning difficulties: word reading ($r = 0.683$), improved ability to divide attention ($r = 0.676$), and reduced parental ratings of oppositional behavior ($r = 0.777$), hyperactivity ($r = 0.702$), restlessness ($r = 0.705$), and overall ADHD behavior ($r = 0.665$).
Voigt et al. (2001)[66]	Double-blind, placebo-controlled trial	$n = 63$, 6–12-year-old children with ADHD	345 mg DHA Placebo tablets	17 weeks	CPRS; CBC; TOVA; CCT; plasma phospholipid fatty acid patterns	Plasma phospholipid DHA content of the active group was 2.6-fold higher at the end of the study than that of the placebo group ($d = 2.68$), ($P < 0.001$). However, there was no statistically significant improvement in any measure of ADHD symptoms.
Hirayama et al. (2004)[67]	Double-blind, placebo-controlled trial	$n = 40$, 6–12-year-old children with ADHD	3.6 g DHA/week via fish-oil-fortified foods Control food without fish oil	8 weeks	DSM-IV; two questions on aggression assessed by teachers and parents; visual perception; visual and auditory short-term memory; Developmental Test of Visual-Motor Integration; Continuous Performance Test; Impatience Test	Those in the supplement group did not show improved performance in any of the outcome measures compared with the placebo group.
Antisocial, violent, and criminal behavior						
Hamazaki et al. (1996)[73]	Double-blind, placebo-controlled trial	$n = 41$, 19–30-year-old university students	1.5–1.8 g DHA Placebo tablets	13 weeks	P-F Study, Stroop, dementia detection test	Aggression against others ("extraggression") in the placebo group was significantly increased at the end of the study compared with the start, whereas it was not significantly changed in the DHA group ($d = -1.22$).
Itomura et al. (2005)[70]	Double-blind, placebo-controlled trial	$n = 166$, 9–12-year-old schoolchildren	3,600 mg DHA, 840 mg EPA/week via fish-oil-fortified foods Placebo tablets	13 weeks	HAQ-C, P-FS	Physical aggression in girls increased significantly in the placebo group and did not change in the fish-oil group, with a significant intergroup difference ($P = 0.008$). There were no significant changes in physical aggression in boys. Extraggression did not change in the placebo group but increased significantly in the fish-oil group, with a significant intergroup difference ($P = 0.02$). Effect sizes could not be calculated.

Abbreviations: AA, arachidonic acid; ADHD, attention deficit hyperactivity disorder; ADHD-RS-IV, ADHD-Rating Scale-IV-Parent Version; ASQ, Conners' Abbreviated Symptom Questionnaires; CBC, Child Behavior Checklist; CCT, Children's Color Trails test; CGI, Clinical Global Impression severity scale; CPRS, Conners' Parent Rating Scales; CPT, Conner's Continuous Performance Test; CPT-IP, Continuous Performance Task, identical pairs; CTRS,Conner's Teacher Rating Scale; CTRS-L,Conner's Teacher Rating Scale Revised; DBD, Disruptive Behavior Disorders Rating Scale; DHA, docosahexaenoic acid; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; EPA, eicosapentaenoic acid; fMRI, functional magnetic resonance imaging; GLA, gamma-linolenic acid; HAQ-C, Hostility-Aggression Questionnaire for Children; MABC, Movement Assessment Battery for Children; P-F Study, psychological test that measures aggression, including extra- and intra-aggression; P-FS, Picture Frustration Study; PUFA, polyunsaturated fatty acids; TEA-ch, Test of Everyday Attention for Children; TOVA, Test of Variables of Attention; WISC-III, Wechsler Intelligence Scale for Children – Third Edition; WORD, Wechsler Objective Reading Dimensions; WJ-R, Woodcock-Johnson Psycho-Educational Battery – Revised.

Table 3 **Studies on the effects of micronutrient and omega-3 fatty acid supplementation on cognition and behavior in young adult prisoners in developed countries, with effect sizes calculated (small effect = 0.2; medium effect = 0.5; large effect = 0.8).**

Reference	Study design	Participants	Intervention (daily dosage)	Trial length	Variables measures	Findings
Gesch et al. (2002)[50]	Double-blind, placebo-controlled trial	$n = 231$, young adult prisoners from the United Kingdom	Vitamin/mineral supplement + 80 mg EPA, 44 mg DHA, 1,260 mg ALA, and 160 mg GLA Placebo tablets	2–39 weeks	Governor and minor reports of antisocial behavior, GATB, ECQ, SAS, HADQ	Those in the supplement group committed an average of 26.3% (95% CI 8.3–44.33%) fewer offenses compared with those in the placebo group ($P = 0.03$, two-tailed). Compared with baseline, the effect on those taking the supplements for a minimum of 2 weeks was an average 35.1% (95% CI 16.3–53.9%) reduction in offenses ($P = 0.001$, two-tailed), whereas those receiving placebo remained within standard error.
Zaalberg et al. (2010)[51]	Double-blind, placebo-controlled trial	$n = 221$, 18–25-year-old young adult prisoners from the Netherlands	Vitamin/mineral supplement + 400 mg DHA, 400 mg EPA, and 100 mg GLA Placebo tablets	4–13 weeks	AQ Dutch version, GHQ-28, SCL-90, SDAS	A significant reduction in the number of reported incidents in prisoners who received the supplement compared with those who received placebo ($P = 0.017$, one-tailed). Other assessments revealed no significant reductions in aggressiveness or psychiatric symptoms.

Abbreviations: ALA, alpha-linolenic acid; AQ, Aggression Questionnaire; CI, confidence interval; DHA, docosahexaenoic acid; ECQ, Emotional Control Questionnaire; EPA, eicosapentaenoic acid; GATB, General Aptitude Test Battery; GHQ-28, General Health Questionnaire-28; GLA, gamma-linolenic acid; HADQ, Hospital Anxiety & Depression Questionnaire; SAS, Survey Anger Scales; SCL-90, Symptom CheckList; SDAS, Social Dysfunction and Aggression Scale.

concerning the effects of the vitamin and mineral supplement on this definition of intelligence.

In 1990, another study[28] was conducted among 86 schoolchildren in Scotland to replicate and address the criticisms of the Welsh study. This study used the same measure of nonverbal intelligence as the Welsh study as well as three other measures of nonverbal intelligence. A nonsignificant difference between the placebo and supplementation groups was found in one nonverbal intelligence test after 7 months of supplementation. In comparison with the Welsh study,[25] which found a significant net gain of 8 IQ points above the placebo group, this study found a nonsignificant gain of only 2.4 IQ points above the placebo group. This direction of effect was not consistently seen with three other tests of nonverbal reasoning. The authors did not clearly conclude whether vitamin and mineral supplementation improved performance. The findings of this study may be limited, as numerous group-administered tests of nonverbal intelligence were used rather than individually administered IQ tests with higher reliability, like the WISC-R.[29]

The largest of these replication studies was conducted in 1988 among 154 schoolchildren in North London.[30] The children were pre- and post-tested on the AH4 part I and part II and the WISC-R after a supplementation period of 4 weeks. As would be expected, the scores on the retests were higher than the original scores in both groups, probably due to practice effects. However, there were no significant differences in performance effects between the supplement and placebo groups in verbal test scores ($d = 0.01$), nonverbal test scores ($d = 0.04$), digit span scores ($d = 0.17$), and coding scores ($d = 0.01$), with very small effect sizes. Again, a major limitation of this study is its very short supplementation period. There is little or no evidence in the literature regarding the time required for vitamin and mineral supplements to absorb into the body and take effect on the brain. This makes it difficult to determine the appropriate amount of time before post-testing participants. The 4-week studies reviewed here indicate that this timeframe may be too short to detect effects.

Despite these negative findings, a number of studies subsequent to the original Welsh study have reported positive responses to supplementation on measures of intelligence. A study conducted in 1991 among 47 children from two schools in England found that, after 6 weeks of supplementation in one school and 8 weeks in the other, the IQ of those receiving vitamin and mineral supplementation significantly increased by 7.6 points, while the placebo was associated with a decline of 1.7 points overall ($d = 0.63$).[31] These changes were mainly of nonverbal rather than verbal measures. The supplement group showed improved performance compared with the placebo group in two of the nonverbal measures of the British Ability Scale – recall of digits ($d = 0.89$) and matrices ($d = 0.59$) – and these effect sizes were medium to large. The verbal subscale measures were calculated for each of the two schools; the supplement groups in both school 1 and school 2 showed increased performance in verbal similarities, but with lower effect sizes compared with the effects on nonverbal tests ($d = 1.03$, $d = 0.39$), respectively. In the naming vocabulary subscale, the supplement group in school 1 showed improved performance ($d = 0.82$), while performance declined in school 2 ($d = -0.09$). The discrepant findings between schools may be due to differences in socioeconomic status. School 1 was described as being located in an area of social deprivation, with some parents being unemployed, while the occupations of the parents of school 2 (described by teachers and the children) were mainly skilled manual and white collar workers. In addition, children who took the supplement were reported as significantly more likely to concentrate and less likely to fidget on a frustrating television task compared with the placebo group in both schools.

A significant effect of vitamin and mineral supplementation on nonverbal intelligence was found in 1991 among 410 schoolchildren in California.[32] The participants were randomly assigned to one of four treatment groups: placebo, 50%, 100%, or 200% of the US Recommended Daily Allowance (USRDA) for 12 weeks. Participants were pre- and post-tested on various measures of verbal and nonverbal intelligence. There were no significant group differences in verbal intelligence on the WISC-R; there was, however, a statistically significant difference of a 3.7-point gain on nonverbal intelligence between the placebo group and the 100% supplement group ($d = 0.49$). The researchers investigated whether the effect found was caused by most of the children gaining approximately 3.7 points or a small proportion of children producing large gains. Results showed that "responders" (described as increasing by 15 points or more in nonverbal IQ after supplementation) contributed most to the net gain. Blood samples were assayed for nutrients pre- and post-supplementation, but these data were not published. Analysis of blood samples would have helped to determine if the children producing the large gains in IQ had lower nutrition levels or a greater increase following supplementation. Another limitation of this study is that the significant result could be attributed to failure to adjust for multiple comparisons in the use of three experimental groups and several measures of intelligence. The authors offer no explanation as to why the 100% supplement is superior to the 50% or 200% supplement but question whether the USRDAs are too low (given that the 100% RDA in the supplement is in addition to dietary nutrient intake). They also questioned whether the 200% supplement did not do as well as the

100% supplement due to an excess of nutrients and recommended future studies to investigate these findings further. It should be considered that findings may vary according to the baseline nutritional status of the population in question.

Importantly, some research has indicated that the effects of vitamin and mineral supplementation can be moderated by nutritional status, with the greatest effects seen among those with lower nutritional status.[29,33–36] Some studies describe their participants as being poorly nourished,[29,35,36] while other studies have performed blood sample analyses pre- and post-supplementation to support their claims.[33,34] In 1997, a study among 30 schoolchildren in England reported a significant difference in increased nonverbal IQ scores between the supplement and placebo groups after 10 weeks of supplementation; however, there was no difference in improved verbal IQ scores on a scale of 100.[36] The children in this sample were described as being at a particular disadvantage because they had less-than-adequate diets and were subject to high levels of pollution, both of which are likely to affect cognitive performance.[37,38] A possible explanation as to why the vitamin and mineral supplementation increased nonverbal but not verbal IQ may be explained by an analysis of the mean rates of errors and omissions on the intelligence tests completed at the beginning of the trial (December) and after 10 weeks of supplementation (March). In the first test, the supplemented group omitted an average of 17.73 nonverbal IQ questions out of a possible 100, which left room for their scores to improve, as can be seen by the drop in omission rate to a mean of 2.45 in the second test. The error rate in the supplemented group did not change significantly at 10 weeks, and participants completed considerably more questions without loss of accuracy on the second test, thus improving their nonverbal IQ scores. For verbal IQ, error rates did not change significantly, but the children were unable to complete any more questions in the second test than in the first test because the original omission rate was so low (mean of 1.5). The authors concluded that there was no room for improvement in verbal IQ due to ceiling effects.

A Belgian study[35] conducted in 1990 among a group of 167 children found a significant positive effect, following a 5-month supplementation period, on nonverbal intelligence in a subgroup of 35% of boys who were described as having a "poor" diet as determined by the number of times vitamin and mineral intakes fell below 50% of the recommended daily intake based on a 15-day dietary diary. The majority of these boys were from less economically privileged areas and from schools for the less academically able. Interestingly, the girls did not respond to supplementation; similar studies have not reported positive response to supplementation as being specific to males. The authors question whether the poorer diets of the boys may have influenced these results.

In 2000, a trial in 245 American schoolchildren reported that 3 months of vitamin and mineral supplementation raised the nonverbal IQ of some but not all groups of schoolchildren; the authors concluded this finding might be attributable to the fact that the majority were already adequately nourished.[29] There was a significant difference of a 2.5-IQ point gain between children who were given vitamin and mineral supplement and children who were given placebo ($d = 0.17$). Further inspection revealed that a significantly higher proportion of children receiving the supplement gained 15 or more IQ points (1 standard deviation) compared with the placebo group. The authors proposed that the increases in IQ seen in only a subgroup rather than in the entire sample may be explained by the children suffering from nutritional deficiencies responding positively to supplementation, not the majority of children who were already adequately nourished. Nevertheless, diet and blood nutrient levels were not measured, so this supposition cannot be confirmed.

In 1991, among 26 adolescent delinquents, those in the supplement group produced significantly larger gains in nonverbal intelligence (+6 points) than the placebo group (−1 point) ($d = 0.48$) following 13 weeks of supplementation.[33] Participants who showed an improvement in blood nutrient concentrations after supplementation showed a significantly greater increase in nonverbal IQ scores (+11.6 points) compared with those whose blood concentrations remained unchanged (−2.7 points) ($d = 1.01$). The findings from this study support suggestions that vitamin and mineral supplementation may improve performance on tests of nonverbal intelligence, and that the greatest improvements can seen in those with low blood nutrient concentrations.

In 1997, a study among 62 incarcerated juveniles was conducted to determine whether vitamin and mineral supplementation could improve their violent and antisocial behavior.[34] After 13 weeks of supplementation, there was a significant difference between the supplement and placebo groups for violent and nonviolent antisocial behavior, with a net 28% difference in rule infractions. Twenty-six participants agreed to donate pre- and post-intervention blood samples. Among 10 participants who maintained their low or normal blood nutrient concentrations, there were no improvements in violence (39 violent acts during baseline and 37 during intervention); however, those participants who corrected their low blood nutrient concentrations during the intervention showed a substantial decline in violence (131 violent acts during baseline compared with 11 during intervention). It

would be beneficial for further studies to investigate whether similar changes in behavior can be seen in other juvenile populations at risk of poor nutrition and antisocial behavior.

In 2000, a study in the United States investigated the effects of vitamin and mineral supplementation on the cognitive and behavioral performance of 20 children with learning disabilities.[39] A randomized, double-blind, placebo-controlled trial was conducted following 1 year of open-label nutrients. Only those children who showed improvements in the open-label trial were eligible for the controlled phase of the study. Following open-label treatment with vitamin and mineral supplements, there were no significant differences in measures of IQ, but within a few weeks or months the children showed significant improvements in academic and behavioral outcomes. In the first year of treatment, the authors claim that some children gained 3 to 5 years in reading comprehension, all of their grades increased significantly, and all 17 who were in special education classes moved to mainstream classes in at least two subjects. Given this part of the study was open label, these improvements could, at least in part, be attributed to a halo effect. The authors suggest that the nutrients do not improve the capacity itself (i.e., IQ) but help the children to fulfill their capacity. Twelve children completed the 1-year double-blind phase, which consisted of four rotations of 2 months each, with random assignment to starting on either the supplement or placebo. After this phase, almost half of the children chose to remain on the nutrients for an additional 2 years. For those who discontinued the trial, it took at least 1 year to see the first indications of a decline in academic performance, while for children who remained on nutrients, the academic gains continued on an upward trend. At the end of year 4, the difference in scores between those who had continued versus those who had discontinued the supplements reached statistical significance and produced a very large effect ($d = 1.88$). While the findings from this study indicate possible benefits of prolonged nutrient supplementation and suggest it can improve academic outcomes in children with learning disabilities, the small sample size limits the generalizability of the results. Given that nutrition is essential for brain function, it is possible that children with learning disabilities have suboptimal nutrient levels that contribute to their difficulties and make them more likely responders. This needs to be explored further.

In 2007, a trial provided 396 children in Australia with a fortified drink containing multiple micronutrients with or without docosahexaenoic acid (DHA) for 12 months. There was a significant positive effect on verbal learning and memory factor (tests loading on this factor: Rey Auditory Verbal Learning Test-A3, Rey Auditory Verbal Learning Test – learning slope, Rey Auditory Verbal Learning Test – delayed recall) in the micronutrient (with or without DHA) groups ($d = 0.23$).[40] There were no significant effects on the tests measuring general intelligence or visual attention. There were no effects of DHA and eicosapentaenoic acid (EPA) on the factors of cognitive tests. This may have been because the n-3 PUFA content was very low (88 mg DHA and 22 mg EPA). These children were recruited from South Australian government metropolitan schools of higher socioeconomic status in Adelaide and were adequately nourished, on average, at baseline according to current indices as indicated by the mean micronutrient concentrations from blood sample analyses. Given that existing evidence suggests micronutrient interventions are most likely to be effective among children whose blood nutrient levels are suboptimal, it is possible that the improved outcomes were attributable to children who were less well nourished, considering that Australian children on the whole are not meeting recommended dietary guidelines, and/or that being "adequately" nourished does not equal "optimally" nourished when it comes to optimal brain function. There were some methodological limitations that may have affected the results of this study. For example, even though the number of outcome variables was reduced by factor analysis, it cannot be concluded that these findings were not due to chance. The authors question whether the observed improvements in performance were due to improved iron status as indicated by the increased serum ferritin concentrations and body iron stores. However, the complete blood sample analysis showed that other nutrient concentrations, such as erythrocyte folate and vitamin B12, also increased, so this possible explanation can only be a speculation.

More recently, in 2010, the effect of vitamin and mineral supplementation on outcomes such as academic performance and learning in schools was investigated. This study was conducted among 684 schoolchildren in the United States from schools described as being located in low-income communities.[41] After 39 weeks of supplementation, the supplement group showed no significant improvement for Terra Nova National Percentile Scores (a standardized achievement test administered by the State of New Jersey) compared with the placebo group ($d = 0.05$), nor did the supplement group show any significant improvements in secondary outcome measures, including number of days absent from school ($d = 0.03$), tardiness ($d = 0.04$), grade point average ($d = 0$), language ($d = -0.12$), mathematics ($d = -0.10$), science ($d = -0.12$), or social science ($d = 0$). While the authors concluded that vitamin and mineral supplementation did not lead to improved school performance, there are some methodological issues that need to be considered. Specific amounts of nutrients in the supplement were not listed, but rather the supplement was described as being similar

to a standard children's multivitamin supplement that provided 100% of the recommended daily values established by the US Food and Drug Administration for ages 4 to 12 years of most vitamins and minerals, with the exception of calcium, magnesium, copper, and iron, which were 12.5%, 18%, 50%, and 50% of the recommended daily values, respectively. Blood samples were not measured, so the nutritional status of participants – as well as whether the supplement improved blood nutrient levels – was unknown. The final analysis was performed on only the participants who completed all five components of the Terra Nova assessment (20% of placebo participants and 27% of multivitamin participants missed at least one component). Lastly, the generalizability of these findings may be limited because the participants were all recruited from a parochial school system.

In sum, a number of studies indicate that, on average, children in developed countries receiving vitamin and mineral supplementation may perform better in tests of nonverbal intelligence and on behavioral measures than children receiving placebo. There are numerous possible reasons as to why vitamin and mineral supplementation may be beneficial to nonverbal (fluid) intelligence and not verbal (crystallized) intelligence. Firstly, it could be argued that nonverbal tests are more sensitive to detect subtle differences compared with tests of verbal intelligence. Secondly, as crystallized intelligence relies on accessing information from long-term memory, it may take longer to show significant differences in learned skills and knowledge after nutritional supplementation than for other cognitive areas, and the length of trials may have been too short to show effects. Thirdly, it is possible that environmental factors such as parenting style, socioeconomic status, and education may be more important influences on crystallized intelligence than nutritional status,[42] although, as suggested above, as capacity increases with nutritional supplementation, these benefits for crystallized intelligence may be seen over longer periods.

For studies that did not find significant results, there are a number of methodological considerations that may account for this. Importantly, several of the studies with null findings were conducted over smaller periods and therefore may not have been adequately long to detect effects.[26,30] It is also important to note that, while most of the studies reviewed used common supplement formulas, the doses varied. The mineral selenium was included in the supplement in one study that reported positive results,[32] while it was not present in supplements used in other studies that reported similar effects.[25,35] Two of the studies that did not find significant results used lower dosages of folate (100 μg)[28,30] compared with several studies reporting positive outcomes using double or more than double that amount.[29,31–33,35,39] Folate contributes to the formation of compounds involved in brain energy metabolism,[43] can heighten serotonin function by slowing destruction of brain tryptophan,[44] and is proposed to be one of the most important vitamins to behavior and academic performance.[45] Studies reporting no significant outcomes used lower dosages of iron (1.3 mg)[28,30] compared with studies that found significant positive outcomes with higher dosages (ranging from 2.4 mg to 18 mg).[29,31–33,35,40] Iron is an essential cofactor in the production of adenosine triphosphate (ATP) energy in the brain, plays an essential role in hemoglobin for ensuring there is sufficient oxygen in the brain for oxidative metabolism, and functions in the enzyme system involved in the production of serotonin, norepinephrine, epinephrine, and dopamine.[44]

Studies that did not find significant results may have been performed in samples that were already well nourished and therefore had no room for improvement. In support of this, studies that assessed blood nutrient concentrations found larger treatment effects in participants who had lower blood nutrient levels pre-supplementation versus post-supplementation.[33,34] As several of the studies reviewed found significant treatment effects in populations described as living in disadvantage,[35,36,46] future research should examine outcomes in children and adolescents who have a low socioeconomic status and/or may be suffering from suboptimal nutritional levels to determine the impact of vitamin and mineral supplementation on their cognition, learning, and behavior. Closer attention may also need to be given to the definition of being adequately nourished. There are suggestions that suboptimal levels of nutrients may manifest in psychological functioning before physical deficiency signs are manifested.[47] A small number of studies have investigated the effects of micronutrient supplementation in addition to PUFAs[48–51] and will be outlined in the discussion on n-3 PUFAs below.

Effects of n-3 PUFAs on cognition, learning, and behavior

Importance of n-3 PUFAs for the brain. The long-chain n-3 PUFA, DHA, is essential for normal brain structure, development, and function.[52,53] DHA is highly concentrated in gray brain matter, composing around 15–20% of the lipids in the brain.[53] n-3 PUFAs are "essential" fatty acids because they cannot be synthesized in the body and therefore must be obtained from the diet. The incorporation of n-3 PUFAs in the brain increases membrane fluidity, which enhances the transmission of neuronal information.[54,55] Evidence from animal studies suggest it can take 2 to 3 months for n-3 PUFAs to be incorporated into brain tissue and for animals to begin showing improvements in learning and/or behavior.[56,57] Human studies have shown that 3 months may be necessary

to see improvements,[58] with effects continuing over 6 months without plateauing.[48] Other studies have shown prolonged effects of n-3 PUFA supplementation on erythrocyte membranes, with erythrocyte DHA concentrations not returning to baseline concentrations after more than 18 weeks following the cessation of treatment.[59,60]

Interventions. In addition to micronutrients, research has investigated the role of n-3 PUFAs in learning, attention, and behavior. Significant effects have been found in subgroups with behavior problems, learning difficulties, and neurodevelopmental disorders.[61–65] In particular, there has been a lot of interest in the effects of n-3 PUFA supplementation on children with attention deficit hyperactivity disorder (ADHD). Existing studies have produced mixed and inconclusive results, with some reporting positive outcomes from n-3 PUFA supplementation and some reporting no significant effects. The discrepancies in these findings may be explained by a range of factors that include differences in trial length, participant inclusion criteria, supplement dose and type (i.e., DHA, its precursor EPA, or combinations of oils), and the type of evaluation methods used.

Two studies used pure DHA supplements.[66,67] The first of these studies was conducted in 2001 and reported no statistically significant improvement in any measure of ADHD symptoms after 4 months; however, all children ($n = 63$) were taking psychostimulant medication during the study period, including the time at which parents completed the subjective measure of ADHD symptoms. This may have influenced the results by suppressing their symptoms and making it difficult to detect any improvements, particularly given that their *t* scores on parent ratings of behavior were in the normal range at baseline. The second study was conducted in 2004 ($n = 40$) and found no significant treatment effects on ADHD symptoms; however, the study duration was 2 months, which may have provided insufficient time to observe any treatment effects. Furthermore, this sample was recruited from Japan, a country with high fish intake, and it is possible that baseline levels were already sufficiently high. Fish intake and blood samples were not reported, so it is unclear whether this was the case. Therefore, conclusions from this study sample cannot be generalized to populations in countries with lower fish intakes.

Several randomized controlled studies have produced results suggesting that PUFA supplementation can improve cognition and behavior in children and adolescents with ADHD symptoms and/or learning difficulties. In 2003, a study conducted in the United States gave 50 children with ADHD symptoms either a PUFA supplement or placebo daily for 4 months.[68] PUFA supplementation resulted in substantial increases in the concentrations of EPA, DHA, and α-tocopherol in plasma phosopholipids and erythrocyte total lipids. There were significant improvements in several outcomes (rated by parents) in both groups, but there was no clear benefit from PUFA supplementation for all behaviors characteristic of ADHD. Only two of 16 outcome measures showed significant improvements: conduct problems rated by parents and attention problems rated by teachers. This could be attributable to the small sample size of 50, with 17 dropouts. Authors did report that increased DHA levels were associated with improved teacher ratings of attention. In a larger trial, PUFA supplementation resulted in a greater number of improvements in defiant behavior from a clinical to a nonclinical range compared with placebo. In 2005, the Oxford-Durham trial[63] found significant improvements following fish oil supplementation in a group of 117 children with dyspraxia and learning difficulties compared with placebo in reading ($d = 0.41$), spelling ($d = 0.34$), and behavior ($d = -0.61$) over 3 months of treatment, producing medium effect sizes. Similar changes were seen in the placebo group after crossover to active treatment, while children who continued with the active treatment maintained or improved their progress. One-third of these children had ADHD symptoms in the clinical range.

In 2007, a study conducted in South Australia[48] found that, in a sample of 132 children, all with ADHD symptoms in the clinical range, 15 weeks of PUFA supplementation resulted in significant improvements and moderate to large effects in parent ratings of core ADHD-related behavioral and cognitive difficulties, including cognitive problems/inattention ($d = 0.52$), ADHD Index ($d = 0.59$), restlessness/impulsiveness ($d = 0.45$), and both *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) subscales (inattention [$d = 0.61$], and hyperactivity [$d = 0.20$]), as well as in ratings of oppositional behavior ($d = 0.43$) compared with placebo. There were no effects on teacher ratings. Following a one-way crossover to active treatment for a further 15 weeks, the placebo group showed significant improvements that were comparable with those of the active groups in the first 15 weeks. Results also revealed improvements among the PUFA groups in a test of the ability to switch and control attention ($d = 0.43$) compared with the placebo group after 15 weeks.[49] This improvement was again seen in the placebo group after being switched to the PUFA supplement from weeks 16 to 30. There were no reported additional benefits of micronutrients, over and above the PUFAs, on cognitive outcomes in this study; however, as discussed by the authors, it is likely that the micronutrient dosages were insufficient.

More recently, in 2009, a study conducted in Sweden[62] among 75 adolescents with ADHD found a greater reduction in ADHD symptoms in the supplement group compared with the placebo group after subjects received daily PUFA supplementation for 3 months; in addition, ADHD-RS scores ($d = -0.36$) and measurements of inattention ($d = -0.31$) and hyperactivity/impulsivity ($d = -0.29$) improved in the supplement group. Baseline Clinical Global Impression (CGI) severity scale scores decreased significantly in the supplement group compared with the placebo group, with a moderate to large effect ($d = -0.64$). A subgroup of 26% of this sample responded with a clinically meaningful reduction in ADHD symptoms and had a drop in CGI scores from moderate/marked severity to near normal compared with placebo, with the results markedly more pronounced in children with the attentive subtype and learning difficulties. Another recent study[69] indicated there were no significant differences between supplement groups in the primary outcomes of cognition, literacy, and parent-rated behavior among 54 children with ADHD with and without learning difficulties after a 4-month fish oil intervention. However, increased DHA blood levels were significantly associated with improvements in word reading ($r = 0.394$) and with reduced parent ratings of oppositional behavior ($r = 0.392$) in the whole sample. Effects were much stronger in a subgroup of 17 children with learning difficulties, as evidenced by the following measurements: word reading ($r = 0.683$), improved ability to divide attention ($r = 0.676$), and reduced parent ratings of oppositional behavior ($r = 0.777$), hyperactivity ($r = 0.702$), restlessness ($r = 0.705$), and overall ADHD behavior ($r = 0.665$). Although these effect sizes are large, the study was underpowered and the between-group comparisons were not statistically significant.

Studies have also investigated the impact of n-3 PUFAs intake on antisocial, violent, and criminal behavior. Several studies reported decreased hostility and aggression after supplementation.[70–72] A study conducted in 1996 among 41 university students in Japan[73] reported that scores in aggression towards others ("extraggression") significantly increased in the placebo group and decreased (not significantly) in the supplemented group after 3 months ($d = -1.22$), which happened to coincide with the students' final examination period. The authors conclude that DHA intake may prevent aggression at times of stress. In 2005, the same research group performed another study to investigate whether fish oil supplementation affected aggression in 166 Japanese schoolchildren.[70] Following 3 months of supplementation, physical aggression in girls increased significantly in the placebo group and did not change in the fish oil group, with a significant intergroup difference with baseline used as a covariate. Interestingly, there were no significant changes in physical aggression in boys. Extraggression did not change in the placebo group but increased significantly in the fish oil group, with a significant intergroup difference with baseline used as a covariate. These findings are different from what could be expected from the results of these authors' previous studies, in which levels of extraggression were lower in the DHA group than in the placebo group. These discrepant findings may be due to lack of a major stressor in the study among schoolchildren, in contrast to the study among university students taking exams. Another methodological issue that could have affected the results is the significantly lower baseline values of extraggression in the fish oil group than in the placebo group. These studies were also conducted in Japanese participants, who typically have a high fish intake and therefore may not benefit from PUFA supplementation.

A recent study conducted among 33 healthy boys for 8 weeks found improved brain activation during performance of a sustained attention task in those who received low-dose or high-dose DHA supplementation, changes that were not apparent in the placebo group.[74] This result is important because it indicates that, even among healthy samples, dietary DHA intake is a modulator of functional cortical activity. Thus, these findings could apply to general populations of schoolchildren, especially given that Western dietary patterns do not provide adequate levels of n-3 PUFAs.[75] The duration of the DHA intervention, however, was quite short (8 weeks); the authors suggest that even larger changes in brain activity patterns may have occurred with a longer DHA supplementation period (i.e., 3 months as suggested by other studies to observe improvements). The main limitation of this study is its small sample size, and, consequently, it may not be a representative sample of this age group.

Two randomized, placebo-controlled studies have investigated the effect of n-3 PUFA and multivitamin-mineral supplementation on behavioral outcomes in young adult prisoners. The first study, conducted in 2002 among 231 young adult prisoners, reported significantly reduced reprimands and violent behavior (a net reduction of 26%) in prisoners taking the active supplements compared with those taking placebo.[50] Further analysis with those who complied with taking the supplement for a minimum of 2 weeks ($n = 172$) showed a 35.1% average reduction in disciplinary incidents, while the corresponding reduction in the placebo group was only 6.7%. These results were replicated in a similar study in 2010, in a Dutch prison in a comparable group of 221 young offenders.[51] There was a significant reduction in reported aggressive and rule-breaking incidents by those who received a supplement containing vitamins, minerals, and PUFAs compared with those who received placebo over a period of 1–3 months. This amounts to a reduction of

34% in the supplement group (similar to that of the UK study) compared with a 14% increase in the placebo group. There were, however, no significant improvements in the number of other (self-reported) outcome measures, and the authors suggest that the results be interpreted with caution. It is possible that many of the prisoners from these two studies had better dietary status during their time in prison compared with when they were living outside of the prison. The provision of regular meals may have masked a potentially stronger effect of supplementation on outcomes measured. Neither of these studies included biochemical measures of nutritional status of the participants before or after intervention, thereby limiting the possibilities to interpret results. Collecting such information could provide better understanding into how improvement in nutritional status is associated with less aggressive and antisocial behavior. It would also be beneficial to investigate whether these findings can be observed in comparative populations that may be living in disadvantage or suffering from nutritional deficiencies.

In summary, several large randomized controlled trials provide evidence to suggest that children respond positively to PUFA supplementation, with effects up to $d = -0.64$ seen in ADHD-type symptoms and/or learning difficulties. Evidence also suggests that young prisoners with antisocial behavior respond positively to supplementation, with significantly fewer reprimands, particularly for violent behavior, in the supplemented groups compared with the placebo groups. The largest single effect of PUFA supplementation was found in aggressive behavior ($d = 1.22$). As Table 1 shows, the type of tests used varies greatly across studies. Several studies have reported improvements in outcomes assessed by teachers and parents; however, cognitive assessments detected little or no improvements. Interestingly, the Oxford-Durham trial[63] detected significant improvements in reading and spelling outcomes, and while the prison-based study in the United Kingdom[50] reported no significant improvements in cognitive or psychological outcomes after supplementation, there were significant improvements in antisocial and violent behavior. The latter findings represent meaningful, real-life outcomes and highlight that the inclusion of different types of outcome measures needs consideration.

The studies reviewed used supplements containing varying amounts of DHA and/or EPA. Several of the studies reporting positive outcomes[48,63,68] used higher dosages of DHA + EPA (558 mg EPA + 174 mg DHA, 558 mg EPA + 174 mg DHA, and 400 mg DHA + 80 mg EPA, respectively), while the studies that did not report positive findings[66,67] used supplements containing predominantly or exclusively DHA (345 mg DHA, 514 mg DHA + 100 mg EPA, respectively). While this may suggest that EPA is more effective in producing positive outcomes than DHA, these studies had other methodological flaws, as explained above. The one study that compared high-DHA supplements with high-EPA supplements found that increased blood levels of DHA were associated with positive outcomes.[69] Interestingly, the study among young adult prisoners from the United Kingdom[50] used very small dosages (44 mg DHA + 80 mg EPA) yet reported significant effects. This study also included a multivitamin-mineral supplement; therefore, the degree to which the n-3 PUFAs contributed to the observed improvements is unclear. It would be beneficial for future studies to measure baseline and post-supplementation n-3 PUFA levels via blood phospholipid samples, as such levels may be a major contributor to differences in findings between studies. These measurements would also assist researchers and practitioners in identifying likely responders.

CONCLUSION

In conclusion, the majority of the research described above suggests that supplementation with vitamins, minerals, and/or essential fatty acids may positively influence nonverbal intelligence, cognitive abilities, learning, and behavioral outcomes in children and adolescents/young adults. The largest treatment effects are seen in trials with durations of at least 3 months and in subgroups of children with low socioeconomic status, learning disabilities, and ADHD or ADHD-type symptoms. Most of the studies that analyzed blood samples for nutrients reported that participants with lower nutrient concentrations in blood were more likely to respond to supplementation than those who were adequately nourished. A variety of cognitive measures have been used across the studies, with some of the earlier studies receiving criticism of the reliability and validity of the measures used. Given the studies reporting significant improvements in antisocial behavior and violence among offenders and in reading and writing in schoolchildren, future studies should focus on real-life, school-based outcomes such as academic achievement, school grades, reprimands, suspensions, and detentions, as such data will provide practical, meaningful data in a population setting. A recurrent recommendation from the studies reviewed is for future research to assess blood nutrient levels pre- and post-intervention to determine whether it is only those suffering from nutritional deficiencies who respond positively to supplementation.

The associations among socioeconomic background, dietary patterns, and blood micronutrient status should be considered. Varying periods of supplementation have been used, and shorter trials appear less likely to produce improvements. There are some indications of continued

improvement over longer periods of supplementation, which could be addressed with longer trials containing multiple assessment points to determine how long it takes for any improvements to plateau, and then to investigate the longer-term effects of ceasing supplementation. It would also be highly beneficial to establish which particular nutrients and doses are most effective in producing positive cognitive, learning, and behavioral outcomes. It is interesting to note that a double-blind controlled trial conducted in China in children from low-income families found that, after 10 weeks of supplementation with either zinc alone, zinc with micronutrients, or micronutrients alone, cognitive outcomes were most improved in the group that received zinc and micronutrients, indicating that a range of nutrients, which work together as cofactors, is important.[76] The practical implication of these recommendations is that they could provide robust evidence for healthcare providers to merit a recommendation to include adequate levels of vitamins, minerals, and essential fatty acids in the diets of children and adolescents to help improve their cognitive and behavioral functioning.

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