

Nutritional and dietary influences on attention deficit hyperactivity disorder

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An abundance of research has investigated causes and treatments for attention deficit hyperactivity disorder (ADHD). The research includes identification of suboptimal levels of nutrients and sensitivities to certain foods and food additives. This review gives an overview of this research and provides an up-to-date account of clinical trials that have been conducted with zinc, iron, magnesium, Pycnogenol, omega-3 fatty acids, and food sensitivities. A literature search was conducted using PubMed, ISI Web of Knowledge, and Google Scholar and included studies published before April 2008. Although further research is required, the current evidence supports indications of nutritional and dietary influences on behavior and learning in these children, with the strongest support to date reported for omega-3s and behavioral food reactions.

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INTRODUCTION

A vast body of literature and research has been focused on attention deficit hyperactivity disorder (ADHD), which is the most prevalent childhood disorder, estimated to affect 2–18% of children¹ depending largely on diagnostic criteria. Core symptoms associated with ADHD are developmentally inappropriate levels of hyperactivity, impulsivity, and inattention. ADHD has a high comorbidity rate with other mental health problems such as anxiety and mood disorders, including depression, suicidal ideation,^{2,3} and bipolar disorder⁴; it is often particularly associated with antisocial problems such as conduct disorder and oppositional defiant disorder.^{3,5,6} When combined with these problems, ADHD can lead to antisocial behavior, substance abuse, and borderline personality disorder in late adolescence and adulthood.^{7–10}

In addition, ADHD is associated with cognitive deficits; it has been estimated that a quarter of these children have a specific learning disability in math, reading, or spelling.¹¹ Attention difficulties are associated with delays in general cognitive functioning, weak language skills, and poor adjustment in the classroom.¹² The disruptive behavior, poor self-discipline, distractibility, and prob-

lems with response inhibition, self-regulation, and emotional control that are associated with ADHD¹³ can adversely impact families, relationships, social interactions, and children's self-esteem and school performance, presenting substantial personal, social, and economic burden for afflicted children, families, schools, and the broader community.

Prevalence of ADHD appears to be on the rise despite increased prescriptions of pharmaceutical medication, particularly methylphenidate and dextroamphetamine. Many parents are concerned about side effects of these medications, and a recent long-term follow-up of the Multimodal Treatment Study of Children with ADHD (MTA) study¹⁴ found that children in their pre-teens who had been medicated with methylphenidate had stunted growth¹⁵ as well as increased risk of juvenile behavior and, possibly, substance abuse.¹⁶

ADHD: CONTRIBUTING INFLUENCES

The etiology of ADHD is complex and is associated with both genetic and environmental factors.³ Studies of twins have provided strong evidence for a genetic component to the disorder, which, in combination with other biological

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Key words: ADHD, food sensitivity, nutrition, omega-3 fatty acids, Pycnogenol

factors, is likely to underlie the neurological deficits that are exacerbated over time by environmental influences.¹⁷ Psychophysiological research has identified neurological abnormalities, particularly in the frontal lobes, in children with ADHD compared with controls.^{18,19} Similarly, a number of studies have identified reduced blood flow to the frontal lobes in children with ADHD.¹⁷ This is consistent with hypotheses that symptoms of ADHD are related to abnormalities in noradrenergic and dopaminergic systems in the frontal lobes.⁷ The high comorbidity of ADHD with a variety of other psychopathologies suggests that these mental health problems share similar underlying neurological mechanisms. This notion is supported by the fact that children with ADHD often have family histories of neurodevelopmental and psychiatric disorders.²⁰

Biological influences that have been associated with ADHD, via their impact on brain development and neurological functioning, include exposure to lead, mercury, and pesticides as well as prenatal exposure to tobacco.^{21,22} In many affected children, there are indications of suboptimal levels of various nutrients and evidence for behavioral reactions to certain foods and food additives. There is particularly compelling evidence that ADHD and other neurodevelopmental disorders such as dyspraxia, dyslexia, and autism may be associated with suboptimal levels of essential fatty acids. Therefore, it may be more prudent to address ADHD symptoms with a nutritional or dietary approach before prescribing medications. The present review evaluates the current state of evidence for the role of nutrients (following a brief overview of nutrition in brain development and function), Pycnogenol, and food sensitivities in ADHD.

NUTRITION AND ADHD

Nutrition and the brain

The brain's critical need for adequate nutrition is demonstrated by effects of malnourishment on the developing brain, including reduced DNA synthesis, cell division, myelination, glial cell proliferation, and dendritic branching. The pathological manifestation of malnourishment will depend on the stage of brain development at the time of nutritional insult.²³ Effects of some nutrient deficiencies on development have become widely known and accepted; for instance, perinatal deficiencies in iodine – now considered the world's most preventable cause of mental retardation,²⁴ folate – related to spinabifida, and iron-related anemia. Severe deficiencies in omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) can result in profound mental retardation associated with peroxisomal disorders.^{25,26}

Less extreme effects of suboptimal nutrient levels on brain development and ongoing function are not as well recognized.

Given the essentiality of an intricate interplay of macro- and micronutrients for optimal brain function, this could result in cognitive and behavioral problems for which the role of nutrition may be overlooked. Although the brain only accounts for 2–2.7% of body weight, it requires 25% of the body's glucose supply and 19% of the blood supply at rest; these requirements increase by 50% and 51%, respectively, in response to cerebral activity.²⁷ Glucose is required for the brain's metabolic activities and is its primary source of energy. The brain has very limited capacity for storing glucose, hence the essentiality of a continuous and reliable supply of blood. A number of nutrients appear to be involved in maintaining cerebral blood flow and the integrity of the blood-brain barrier, including folic acid, pyridoxine, colabamin, thiamine,²⁷ and omega-3 PUFA.²⁸ Neurotransmitters are also an integral component of the brain's communication system; various nutrients are required for monoamine metabolic pathways and act as essential cofactors for the enzymes involved in neurotransmitter synthesis.²⁷

Zinc

As well as playing important roles in immune function, growth, development, and reproduction, zinc is required for the developing brain. It plays numerous roles in ongoing brain function via protein binding, enzyme activity, and neurotransmission. As an essential cofactor for over 100 enzymes, zinc is required for the conversion of pyridoxine (B₆) to its active form, which is needed to modulate the conversion of tryptophan to serotonin; zinc is involved in the production and modulation of melatonin, which is required for dopamine metabolism and is a cofactor for delta-6 desaturase, which is involved in essential fatty acid conversion pathways.²⁹

A comprehensive review of the role of zinc in brain function and in ADHD is provided by Arnold.²⁹ His review includes reports of nine studies conducted in various parts of the world, which all found lower zinc levels in children with ADHD as well as correlations between lower zinc levels and severity of symptoms. One avenue of zinc depletion in these children may be via reactions to synthetic chemicals found in food additives. Twenty hyperactive males who reacted to the orange food dye tartrazine were challenged in a double-blind, placebo-controlled trial with 50 mg of the food additive. Following the challenge, serum zinc levels decreased and urine levels increased in the hyperactive group compared with controls, suggesting that metabolic wastage of zinc occurs under chemical stress. Behavioral and emotional symp-

toms also deteriorated in hyperactive children in association with changes in zinc levels.³⁰

Two clinical zinc supplementation trials have been conducted in children with ADHD. One controlled study found significant improvements in hyperactivity, impulsivity, and socialization scores, but not inattention, after 12 weeks of supplementation with 150 mg zinc per day in children with ADHD compared with controls. It should be noted that this is a particularly high dose of zinc, and there was a high dropout rate in the study (although it was not significantly different between the active and placebo groups).³¹ The other study allocated 44 children who were diagnosed with ADHD to methylphenidate along with either 55 mg zinc sulfate or placebo over 6 weeks to investigate adjunctive benefits of zinc. Scores on parent and teacher rating scales for the children improved in both groups, and these improvements were significantly greater in the zinc group.³²

It is interesting to note that both zinc and free serum fatty acid levels were found to be lower in a group of 48 children with ADHD compared with 45 controls, and that these levels were strongly correlated in the ADHD group.³³ In light of these studies and reports of other nutritional deficiencies in ADHD, the present author conducted a controlled trial (described below), that focused on omega-3 PUFAs and investigated additive benefits of a multivitamin/mineral tablet in conjunction with the PUFA supplement.³⁴ No additional benefits were found with the MVM supplement over and above the PUFA supplement; however, the supplement contained <2 mg zinc, which, when compared to the studies above, is likely to have provided inconclusive results regarding potentially additive benefits of zinc combined with PUFA.

Iron

Anemia from iron deficiency is estimated to affect 20–25% of infants, and many more are thought to suffer iron deficiencies without anemia, putting them at risk for delayed or impaired childhood development. Iron is important for the structure and function of the central nervous system and it plays a number of roles in neurotransmission. Iron deficiency has been associated with poor cognitive development and it has been proposed that iron deficiency may affect cognition and behavior via its role as a co-factor for tyrosine hydroxylase, the rate-limiting enzyme involved in dopamine synthesis.^{35,36}

Iron levels were found to be twice as low in 53 non-anemic children with ADHD compared to 27 controls with no other evidence of malnutrition; specifically, serum ferritin levels were abnormal (<30 ng/mL) in 84% of children with ADHD and 18% of controls ($p < 0.001$). Furthermore, low serum ferritin levels were correlated

with more severe ADHD symptoms measured with Conners' Parent Rating Scales (CPRS), particularly with cognitive problems and hyperactivity.³⁶ A recent study also found low iron levels in 52 non-anemic children with ADHD, and these were correlated with hyperactivity scores on CPRS, although not with a range of cognitive assessments.³⁷ It has been suggested that iron could play a role in ADHD due to its neuroprotective effect against lead exposure.³⁸ Iron deficiency is also associated with restless legs syndrome, which is a common comorbid condition in children with ADHD symptoms, and may, therefore, account for greater variance of symptoms in this subgroup of children.³⁹ Indeed, a recent study found that children with ADHD who suffered from restless legs had lower iron levels than those without restless legs.⁴⁰

An early, uncontrolled pilot study investigated effects of iron supplementation on ADHD symptoms in 14 non-anemic 7–11-year-old boys. After 30 days of daily supplementation with 5 mg/kg ferrous-calcium citrate (active elemental iron, 0.05 mg/kg daily), blood samples showed increases in serum ferritin levels and significant decreases were found on parent ratings of symptoms on Conners' Rating Scales. However, these improvements were not correlated with increased iron levels and no significant improvements were found on teacher ratings. It was concluded that iron supplementation may not be effective in non-iron-deficient children and that it should be investigated in iron-deficient children with ADHD.⁴¹ It is also possible that 30 days may not have been long enough to observe any effects. One report of a case study outlined the effects of iron supplementation on a 3-year-old boy with diagnosed ADHD. This boy did have an iron deficiency and also displayed sleep problems (delayed sleep onset and excessive motility in sleep). After 4 months of iron supplementation, parents and teachers reported mild improvements in the child's symptoms, and marked improvements were reported after 8 months. He also showed enhanced quality of sleep.⁴²

These studies were followed up by a double-blind, placebo-controlled study with 23 non-anemic, 5–8-year-old iron-deficient children (serum ferritin levels <30 ng/mL) with ADHD. Following 12 weeks of supplementation with 80 mg ferrous sulfate per day or placebo, symptoms tended to improve in the treatment group on all ADHD scales and the improvements were significant on two outcome measures. Seventy five percent of children in the treatment group had diagnosed or possible restless leg syndrome and this condition improved in 12 of those 14 children following iron supplementation. These improvements were not seen in the placebo group ($n = 5$).⁴³ This study supports indications that children with low iron levels who have both ADHD and restless legs may be more likely to benefit from iron supplementation.

Magnesium

Suboptimal magnesium (Mg) levels may impact brain function via a number of mechanisms including reduced energy metabolism, synaptic nerve cell signaling, and cerebral blood flow; it has also been suggested that its suppressive influence on the nervous system helps to regulate nervous and muscular excitability.⁴⁴ Low Mg levels have been reported in children with ADHD. In 116 children with diagnosed ADHD, 95% were found to have Mg deficiency (77.6% in hair; 33.6% in blood serum), and these occurred significantly more frequently than in a control group. Magnesium levels also correlated highly with a quotient of freedom from distractibility.⁴⁴ In 50 children aged 7–12 years with ADHD, Mg supplementation (200 mg/day) over 6 months resulted in significant reductions in hyperactivity and improved freedom from distractibility both compared with pretest scores and with a control group of 25 children with ADHD who were not treated with magnesium.⁴⁵ Another open study also found lower Mg levels in 30 of 52 hyperactive children compared with controls, and improvements in symptoms of hyperexcitability following 1–6 months of supplementation with combined Mg/vitamin B₆ (100 mg/day).⁴⁶ A similar study by the same researchers 2 years later found lower Mg levels in 40 children with clinical symptoms of ADHD than in 36 healthy controls. Decreased Mg levels were also associated with increased hyperactivity and sleep disturbance and poorer school attention. After 2 months of Mg/vitamin B₆ supplementation for the 40 children with ADHD, hyperactive symptoms were reduced and school performance improved.⁴⁷ This work indicates the need for controlled studies in children with ADHD and magnesium deficiency.

Omega-3 fatty acids

Sixty percent of the dry weight of the brain is composed of fats, and the largest concentration of long-chain omega-3 PUFA docosahexaenoic acid (DHA) in the body is found in the retina, brain, and nervous system.⁴⁸ There is evidence that DHA is required for nerve cell myelination and is thus critical for neural transmission.⁴⁹ Importantly, DHA levels in neural membranes vary according to dietary PUFA intake.^{49,50} DHA precursor eicosapentaenoic acid (EPA) is also believed to have important functions in the brain,⁵¹ possibly via its role in synthesis of eicosanoids with anti-inflammatory, anti-thrombotic, and vasodilatory properties. Animal studies have associated omega-3 levels with levels of neurotransmitters dopamine and serotonin,^{52,53} we have proposed that one of their primary influences on mental health may also be via improved cerebral vascular function.²⁸

In the 1980s, researchers observed signs of fatty acid deficiency in hyperactive children⁵⁴; thereafter, a number of studies found lower omega-3 PUFA levels in children with ADHD compared with controls.^{55–59} Randomized controlled trials have found equivocal results, which may be explained by variations in selection criteria, sample size, dosage and nature of the omega-3 PUFA supplement and length of supplementation. One study performed in the United States supplemented 6–12-year-old medicated boys with a “pure” ADHD diagnosis (without comorbidities) with 345 mg of algae-derived DHA per day for 16 weeks and found no significant improvements on outcome measures.⁶⁰ Another study in the United States gave 50 children aged 6–13 years with ADHD symptoms and skin and thirst problems 480 mg DHA and 80 mg EPA along with 40 mg arachidonic acid (AA; omega-6 PUFA) daily over 4 months. Significant improvements were only found in conduct problems rated by parents and attention problems rated by teachers; importantly, the latter was correlated with increases in erythrocyte DHA levels.⁶¹ A study performed in Japan using both DHA and EPA found no significant treatment effects of bread enriched with fish oil (supplying 3600 mg DHA and 700 g EPA per week) on symptoms of ADHD in a 2-month, placebo-controlled, double-blind trial with 40 children aged 6–12 who were mostly drug-free (34/40). The placebo bread contained olive oil.⁶² Blood samples were not taken, so it is not clear whether this sample had a baseline deficiency in fatty acids. Given that the study was conducted in Japan, a country known to have high fish consumption, it is possible that they did not. It is also possible that 2 months may not have been a sufficient length of time for effects to become observable. Another pilot study in the United Kingdom supplemented 41 non-medicated children aged 8–12 years who had literacy problems (mainly dyslexia) and ADHD symptoms above the population average with 186 mg EPA and 480 mg DHA along with 42 mg AA per day for 12 weeks; the results showed improvements in literacy and in ADHD symptoms evaluated using Conners’ Rating Scales.⁶³

Since these small trials, the results of two large, randomized, placebo-controlled, double-blind interventions have been published. The first was conducted in the United Kingdom with 117 non-medicated children aged 5–12 years with developmental coordination disorder; a third of these children had ADHD symptoms above the 90th percentile, placing them in the clinical range for a probable ADHD diagnosis. On average, these children were functioning a year behind their chronological age on reading and spelling. Following 3 months of daily supplementation with 552 mg EPA and 168 mg DHA with 60 mg gamma linolenic acid (GLA; omega-6 PUFA), children in the treatment group showed significant improvements in core ADHD symptoms, as rated by teachers on

Conners' Rating Scales. The treatment groups also increased their reading age by 9.5 months (compared to 3.3 months in the placebo group) and their spelling age by 6.6 months (compared to 1.2 months in the placebo group).⁶⁴ A review of the above-mentioned studies was published following the latter trial.⁶⁵

The next study (conducted by the present author) investigated treatment with the same supplement in 132 non-medicated Australian children aged 7–12 years who all had ADHD symptoms in the clinical range for a probable diagnosis. This study also investigated additive benefits of a multivitamin/mineral (MVM) supplement. There were no differences between the PUFA groups with and without the MVM supplement. However, both of the PUFA groups showed significant improvements compared to placebo in core ADHD symptoms, as rated by parents on Conners' Rating Scales over 15 weeks.³⁴ Cognitive assessments found significant improvements in the children's ability to switch and control their attention, and in their vocabulary. Importantly, the latter improvements mediated parent-reported improvements in inattention, hyperactivity, and impulsivity.⁶⁶ The effect sizes of the UK and Australian studies are similar to those reported in a meta-analysis of stimulant medication trials.

Our group is currently following up on these studies by comparing EPA-rich and DHA-rich oils, each providing 1 g omega-3 PUFA per day, on ADHD symptoms and literacy in children with ADHD and learning difficulties; the aim is to identify whether this subgroup with learning difficulties may be more likely to respond to omega-3 supplementation. We are also measuring erythrocyte PUFA levels to gain further information regarding baseline levels, likely responders, and the relative importance of EPA and DHA versus sunflower oil (containing omega-6 PUFA).

Pycnogenol and ADHD

Antioxidants are receiving growing interest for their potential to reduce oxidative stress in the brain, which may contribute to a variety of psychiatric disorders including autism and ADHD.⁶⁷ Pycnogenol is the registered trademark for a potent antioxidant derived from maritime pine bark. It contains concentrated polyphenolic compounds, primarily procyanidins and phenolic acids (for a review of its pharmacology see Rohdewald⁶⁸). Pycnogenol may also increase nitric oxide production and has been reported to improve blood circulation.^{69,70} Therefore, it may assist with cerebral blood flow, which is also thought to be impaired in ADHD.

Several anecdotal reports indicate successful treatment of ADHD symptoms with Pycnogenol.^{71,72} In one case report, parents gave Pycnogenol to their 10-year-old

boy with ADHD following unsuccessful response to stimulant medication. They noted significant improvements in target symptoms over 2 weeks. When they agreed to try him on stimulant medication without the Pycnogenol again, he reportedly became significantly more hyperactive and impulsive and received numerous demerits at school. When Pycnogenol supplementation was reinstated, he again improved within 3 weeks.⁷²

Only two controlled studies with Pycnogenol have been conducted. One compared Pycnogenol with methylphenidate and placebo in a three-way crossover trial with 24 adults aged 24–50 years who met the criteria for ADHD. They were all given 1 mg/lb body weight Pycnogenol per day, methylphenidate (increased gradually from 10 mg to 45 mg per day) and placebo for 3 weeks, each separated by a 1-week washout. No significant improvements were observed in the methylphenidate or the Pycnogenol groups compared with placebo. It is possible that there was no treatment effect in this group or, alternatively, that 3 weeks was not long enough and/or the sample was too heterogeneous and the sample size too small.⁷³

In the other study, 61 children aged 9–14 years with ADHD symptoms [diagnosed as hyperkinetic disorder ($n = 44$), hyperkinetic conduct disorder ($n = 11$), or ADD ($n = 6$)] were randomly allocated to receive 1 mg/kg body weight of Pycnogenol or placebo daily for 1 month and assessed again following an additional month of treatment washout. Significant improvements were observed in the treatment groups after 1 month, as measured by teacher ratings of hyperactivity and inattention, parent ratings of hyperactivity, and visual-motoric coordination and concentration. Symptoms tended to relapse following the 1-month washout.⁷⁴ Importantly, biomarkers of oxidative damage decreased in the treatment group compared with placebo, and this was associated with improvement in symptoms.^{75–77} Further controlled studies are clearly warranted to investigate effects of Pycnogenol on ADHD symptoms in children.

A summary of double-blind, randomized, placebo-controlled nutritional interventions for ADHD, including Pycnogenol, is provided in Table 1.

FOOD INTOLERANCE AND ADHD

In addition to nutritional influences, there is evidence that many of these children react to certain foods and/or food additives. Suggestions of links between diet and behavior go back to the 1920s; they became well-known in the 1970s with the Feingold diet, which focused on eliminating naturally occurring salicylates, artificial food colors, artificial flavors, and the preservative butylated hydroxytoluene.⁷⁸

Table 1 Summary of double-blind, randomized, placebo-controlled trials of nutrition in ADHD evaluating zinc, iron, omega-3 fatty acids, and Pycnogenol.

Reference	Participants	Daily dose	Length of trial	Measures	Outcomes*
Bilici et al. (2004) ³¹	N = 400; mean age 9.4, SD = 1.5 (78% boys). DSM-IV ADHD diagnosis, unmedicated	Zinc: 150 mg zinc sulfate	12 weeks	ADHD Scale (ADHDS); ACTQ; DuPaul Parent Ratings of ADHD	Treatment > placebo: ADHDS; ADHDS-Hyperactivity; ADHDS-Impulsivity; ADHDS-Socialization; ACTQ-Hyperactivity; ACTQ-Conduct. Treatment = placebo on remaining measures
Akhondzadeh et al. (2004) ³²	N = 44; mean age 7.88, SD = 1.67 (59% boys); DSM-IV ADHD diagnosis, medicated	Zinc: 55 mg zinc sulfate	6 weeks	Parent and Teacher ADHD Rating Scales	Treatment > placebo on both measures
Konofal et al. (2008) ⁴³	N = 23; 5–8 year old (78% boys); non-anemic, iron-deficient (serum ferritin levels < 30 ng/mL); met DSM-IV criteria for ADHD; 16 had restless legs	Iron: 80 mg ferrous sulfate	12 weeks	CPRS; CTRS; ADHD rating scale; CGI-S; restless legs	Treatment > placebo on ADHD rating scale and CGI-S; Treatment > placebo on CPRS and CTRS; not significant; Restless legs improved in 12/14 in treatment group
Voigt et al. (2001) ⁶⁰	N = 54; 6–12 years old (78% boys); idiopathic ADHD diagnosis; were being treated successfully with medication	n-3 PUFA: 345 mg DHA	16 weeks	CPRS; CBC; TOVA; CCT	Treatment = placebo on all measures
Stevens et al. (2003) ⁶¹	N = 50; 6–13 years old (78% boys); ADHD diagnosis; high FADS1; some on medication (equally allocated to conditions)	n-3 and n-6 PUFA: 96 mg GLA, 40 mg AA, 80 mg EPA, 480 mg DHA, 24 mg Vit E	16 weeks	DBD; ASQ; CPT; WIJPEB-R; FADS	Treatment > placebo: DBD-Conduct (parents); DBD-Attention (teachers). Other 14 outcome measures non-significant
Hirayama et al. (2004) ⁶²	N = 40; 6–12 years old (80% boys); ADHD diagnosis; 15% medicated; 82% comorbid conditions	n-3 PUFA: 100 mg EPA, 514 mg DHA	8 weeks	DSMV-IV ADHD; DTVP; STM; CPT; Other	Treatment = placebo on all measures (except that placebo > treatment on CPT and STM)
Richardson et al. (2002) ⁶³	N = 29; 8–12 years old (62% boys); normal IQ; low reading ability; above-average ADHD scores on Conners' Index; no participants in treatment for ADHD	n-3 and n-6 PUFA: 864 mg LA, 42 mg AA, 96 mg LNA, 186 mg EPA, 480 mg DHA, 60 µg Vit E	12 weeks	CPRS	Treatment > placebo: CPRS; cognitive problems/inattention; anxious/shy; Conners' global index; DSM inattention; DSM hyperactive/impulsive; Conners' ADHD Index

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Table 1 Continued

Reference	Participants	Daily dose	Length of trial	Measures	Outcomes*
Richardson et al. (2005) ⁶⁴	N = 117; 5–12 years old (77% boys); developmental coordination disorder, 1/3 with ADHD symptoms in clinical range, not in treatment; IQ > 70	n-3 and n-6 PUFA: 60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg Vit E	12 weeks active vs placebo; one-way crossover to active treatment for 12 weeks	MABC; WORD; CTRS	Treatment > placebo: WORD; oppositional behavior; cognitive problems/inattention; hyperactivity; anxious/shy; perfectionism; social problems; Conners' index; DSM-IV inattention, hyperactive/impulsive. Treatment = placebo: MABC [†]
Sinn et al. (2007) ³⁴	N = 132 (questionnaire data available for 104); 7–12 years old (74% boys); ADHD symptoms in clinical range; unmedicated	n-3 and n-6 PUFA: 60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg Vit E	15 weeks active vs placebo; one-way crossover to active treatment for 15 weeks	CPRS; CTRS	Treatment > placebo CPRS: cognitive problems/inattention; hyperactivity; ADHD index; restless/impulsive; DSM-IV hyperactive/impulsive; oppositional. Treatment = placebo on other subscales and CTRS
Tenenbaum et al. (2002) ⁷³	N = 24; 24–50 years old (46% males); ADHD combined type	Pycnogenol: 1 mg/lb body weight	3 weeks on Pycnogenol, methylphenidate and placebo separated by 1-week wash-out	Barkley's ADHD Scale; ADOSA; BDI; BAI; clinical interviews; CSC for AADD; BIS; Brown ADD scales; CPT	Treatment = placebo on all measures
Trebatická et al. (2006) ⁷⁴	N = 61; 6–14 years old (82% boys); hyperkinetic disorder, hyperkinetic conduct disorder, attention deficit without hyperactivity	Pycnogenol: 1 mg/kg body weight	1 month treatment or placebo; 1-month washout	CAP; CTRS; CPRS; PDW	Treatment > placebo: CAP inattention and hyperactivity; CTRS inattention; CPRS hyperactivity; visual-motoric coordination and concentration. Treatment = placebo on remaining subscales

* Positive treatment effects are presented in *italic*.

Abbreviations: n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; ACTQ, Turkish adaptation of Conners' Teacher Rating Scales; ADOSA, Attention Deficit Scales for Adults; CPRS, Conners' Parent Rating Scales; ASQ, Conners' Abbreviated Symptom Questionnaires; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BIS, Barratt Impulsiveness Scale; Brown ADD Scales; CAP, Child Attention Problems; Teacher rating scale; CBC, Child Behavior Checklist; CCT, Children's Color Trails test; CGI-S, Clinical Global Impression-Severity; CPT, Continuous Performance Test; CPT, Conners' Continuous Performance Test; CSC for AADD, Copeland Symptom Checklist for Adult Attention Deficit Disorders; CTRS, Conners' Teacher Rating Scales; DBD, Disruptive Behavior Disorders rating scale; DTVP, Development Test of Visual Perception; FADS, fatty acid deficiency symptoms; MABC, Movement Assessment Battery for Children; Other, 2 questions assessing aggression and 2 questions assessing impulsivity; PDW, Prague Wechsler Intelligence Scale for Children (modified Wechsler Intelligence Scale for Children, WISC); RBPC, Revised Behavior Problem Checklist; STM, short-term memory; TOVA, Test of Variables of Attention; Vit E, vitamin E (α -tocopheryl acetate); WJPEB-R, Woodstock-Johnston Psycho-Educational Battery – Revised; WORD, Wechsler Objective Reading Dimensions.

Behavioral reactions to food substances are associated with pharmacological rather than allergic mechanisms, although it is possible that these reactions coexist.⁷⁹ Underlying mechanisms for behavioral food reactions are not entirely clear. Increased motor activity was identified in neonatal rats following ingestion of red food color;⁸⁰ other early animal studies linked reactions to the nervous system, e.g., similar hyperactive response was identified to dopamine depletion as well as administration of sulfanilic acid, an azo food dye metabolite, in developing rats;⁸¹ dose-dependent increase in red food color may increase the release of acetylcholine into neuromuscular synapses; and colors may affect uptake of neurotransmitters.⁸² In support of animal studies, EEG readings were reported to normalize in nearly 50% of children ($n = 20$) with behavior disorders after starting an elimination diet.⁸³ Behavioral food reactions may be attributable to the presence of metals, including lead, mercury, and arsenic, in food colorings,⁸⁴ which warrants investigation.

Feingold reported that more than half of children who adhered to his elimination diet responded favorably and that many children's behavioral symptoms reached the normal range. It has since been discovered, however, that many of the foods in his diet contained salicylates, and that many of these children also react to other food components such as food coloring.⁷⁹ The complexities of dietary intervention, most notably the large variety of potentially suspect food substances and individual differences in the nature and dosage of the food intolerance, resulted in inconsistencies in subsequent research trials. Many of these studies also had interpretational issues⁸⁵ and methodological limitations involving the formulation of the intervention diet as well as the placebo diet and washout periods between them. Additionally, subsequent research has adapted to increasing knowledge on salicylates and potentially reactive food substances including amines.⁸⁶

Dietary interventions for ADHD and their inconsistent findings have generated a great deal of controversy, as have titles such as "Diet and child behavior problems: fact or fiction?"⁸⁷ However, despite methodological difficulties of measuring dietary complexities and individual variation, a recent review cited eight controlled studies that found either significant improvement following a "few-food" (oligoantigenic) diet compared with placebo or worsening of symptoms in placebo-controlled challenges of offending substances following an open challenge to identify the substance.⁸⁸

A meta-analysis of 15 double-blind, placebo-controlled trials focusing specifically on artificial food colors found that these food additives promoted hyperactive behavior in hyperactive children.⁸⁹ Following this meta-analysis a randomized, double-blind, placebo-

controlled, crossover challenge trial with 153 children aged 3 years and 144 children aged 8/9 years from a general population of children reported significant effects of artificial colors and sodium benzoate preservative on hyperactive behavior.⁹⁰ It should be noted that the food colorings and preservative (or placebo) were delivered in fruit juice containing salicylates, which could have confounded the effects for the more hyperactive children at risk for salicylate sensitivity. It is interesting that this study demonstrated hyperactive effects of food colorings on healthy children from a general population, thus expanding the effects of food colorings beyond children with sensitivities.

CONCLUSION

Research to date indicates that nutrition and diet may have a role in the hyperactivity and concentration/attention problems associated with ADHD in children. In children with suboptimal levels of iron, zinc, and magnesium, there is some support for improvements being achieved with supplementation of these nutrients. There are also indications that supplementation with Pycnogenol might assist with symptoms. However, more well-controlled clinical trials are required. The strongest support so far is for omega-3 PUFA and behavioral reactions to food colorings. Research still needs to determine optimal levels of these nutrients for this group of children and markers of food sensitivity (currently requiring time-intensive dietary challenges) in order to inform clinical practice in the identification of potential deficiencies and/or behavioral food reactions. Suggestions that these children often react to inhaled environmental substances such as petrol fumes, perfumes, fly sprays, and felt pens, also require further investigation.⁸⁶

There are clearly multiple influences on ADHD, including genetic and environmental (parental, social) factors. Whether these constitute different groups of children or whether there is a common underlying component to some or all of these remains to be determined. A recent study found lower omega-3 PUFA levels in 35 young adults with ADHD than in 112 controls, but levels of iron, zinc, magnesium, or vitamin B₆ were not reduced.⁹¹ However, since zinc is required for the metabolism of other nutrients, zinc deficiencies may contribute to suboptimal levels of nutrients such as omega-3 PUFA. In addition, a genetic problem with enzyme production or absorption of nutrients may predispose children to nutrient deficiencies and/or excessive oxidation, thus contributing concurrently to food sensitivities. Adverse genetic, environmental, and nutritional conditions may exacerbate psychosocial factors (e.g., it is easier to parent a child with an easygoing, undemanding personality). In order to provide optimal treatment for these

children, all of these possibilities need to be explored in multidisciplinary, multimodal, research models that take all potential factors into consideration.

Acknowledgment

Declaration of interest. NS is the current recipient of an Australian Research Council Fellowship, with contributions by Novasel Australia, for the 3-year project “Cognitive and behavioral benefits of omega-3 fatty acids across the lifespan”.

REFERENCES

1. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder: a public health view. *Ment Retard Dev Disabil Res Rev.* 2002;8:162–170.
2. Birlleson P, Sawyer M, Storm V. The mental health of young people in Australia: child and adolescent component of the national survey – a commentary. *Australas Psychiatry.* 2000;8:358–362.
3. Root RWI, Resnick RJ. An update on the diagnosis and treatment of attention-deficit/hyperactivity disorder in children. *Prof Psychol Res Pract.* 2003;34:34–41.
4. Biederman J, Faraone S, Mick E, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *J Am Acad Child Adolesc Psychiatry.* 1996;35:997–1008.
5. Colledge E, Blair RJR. The relationship in children between the inattention and impulsivity components of attention deficit and hyperactivity disorder and psychopathic tendencies. *Pers Individ Diff.* 2001;30:1175–1187.
6. Crowley TJ, Mikulich SK, MacDonald M, Young, SE, Zerbe GO. Substance-dependent, conduct-disordered adolescent males: severity of diagnosis predicts 2-year outcome. *Drug Alcohol Depend.* 1998;49:225–237.
7. Biederman J. ADHD across the lifecycle. *Biol Psychiatry.* 1997;42(Suppl):146.
8. Ingram S, Hechtman L, Morgenstern G. Outcome issues in ADHD: adolescent and adult long-term outcome. *Ment Retard Dev Disabil.* 1999;5:243–250.
9. Fossati A, Novella L, Donati D, Donini M, Maffei C. History of childhood attention deficit/hyperactivity disorder symptoms and borderline personality disorder: a controlled study. *Compr Psychiatry.* 2002;43:369–377.
10. Rey JM, Morris-Yates A, Singh M, Andrews G, Steward GW. Continuities between psychiatric disorders in adolescents and personality disorders in young adults. *Am J Psychiatry.* 1995;152:895–900.
11. Pliszka SR. Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: An overview. *J Clin Psychiatry.* 1998;59(Suppl 7):50–58.
12. Warner-Rogers J, Taylor A, Taylor E, Sandberg S. Inattentive behavior in childhood: epidemiology and implications for development. *J Learn Disabil.* 2000;33:520–536.
13. Barkley RA. Issues in the diagnosis of attention-deficit/hyperactivity disorder in children. *Brain Dev.* 2003;25:77–83.
14. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: changes in effectiveness and growth after the end of treatment. *Pediatr.* 2004;113:762–769.
15. Swanson JM, Elliot GR, Greenhill LL, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. *J Am Acad Child Adolesc Psychiatry.* 2007;46:1015–1027.
16. Molina BSG, Flory K, Hinshaw SP, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry.* 2007;46:1028–1040.
17. Bradley JDD, Golden CJ. Biological contributions to the presentation and understanding of attention-deficit/hyperactivity disorder: a review. *Clin Psychol Rev.* 2001;21:907–929.
18. Mann CA, Lubar JF, Zimmerman AW, Miler CA, Muenchen RA. Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: controlled study with clinical implications. *Pediatr Neurol.* 1992;8:30–36.
19. Riccio CA, Hynd GW, Cohen MJ, Gonzalez JJ. Neurological basis of attention deficit hyperactivity disorder. *Except Child.* 1993;60:118–124.
20. Richardson AJ. Clinical trials of fatty acid supplementation in ADHD. In: Glen AIM, Peet M, Horrobin DF, eds. *Phospholipid Spectrum Disorders in Psychiatry and Neurology.* Marius Press: Carnforth. 2003:529–541
21. Curtis LT, Patel K. Nutritional and environmental approaches to preventing and treating autism and attention deficit hyperactivity disorder (ADHD): a review. *J Altern Complement Med.* 2008;14:79–85.
22. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in US children. *Env Health Perspect.* 2006;114:1904–1909.
23. Lecours AR, Mandujano M, Romero G. Ontogeny of brain and cognition: relevance to nutrition research. *Nutr Rev.* 2001;59(Suppl):S7–S11.
24. Hetzel BS. Iodine and neuropsychological development. *J Nutr.* 2000;130(Suppl):S493–S495.
25. Martinez M. Docosahexaenoic acid therapy in docosahexaenoic acid-deficient patients with disorders of peroxisomal biogenesis. *Lipids.* 1996;31(Suppl):S145–S152.
26. Uauy R, Peirano P, Hoffman D, Mena P, Birch D, Birch E. Role of essential fatty acids in the function of the developing nervous system. *Lipids.* 1996;31(Suppl):S167–S176.
27. Haller J. Vitamins and brain function. In: Lieberman HR, Kanarek RB, Prasad C, eds. *Nutritional Neuroscience.* Taylor & Francis Group: Boca Raton. 2005:207–233.
28. Sinn N, Howe PRC. Mental health benefits of omega-3 fatty acids may be mediated by improvements in cerebral vascular function. *Biosci Hypotheses.* 2008;1:103–108.
29. Arnold LE, DiSilvestro RA. Zinc in attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2005;15:619–627.
30. Ward NI, Soulsbury KA, Zettel VH, Colquhoun ID, Bunday S, Barnes B. The influence of the chemical additive tartrazine on the zinc status of hyperactive children – a double-blind placebo-controlled study. *J Nutr Environ Med.* 1990;1:51–57.
31. Bilici M, Yildirim F, Kandil S, et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 2004;28:181–190.
32. Akhondzadeh S, Mohammadi M-R, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. *BMC Psychiatry.* 2004;4:9
33. Bekaroglu M, Aslan Y, Gedik Y, et al. Relationships between serum free fatty acids and zinc, and attention deficit

- hyperactivity disorder: a research note. *J Child Psychol Psychiatry*. 1996;37:225–227.
34. Sinn N, Bryan J. Effect of supplementation with polyunsaturated fatty acids and micronutrients on ADHD-related problems with attention and behavior. *J Dev Behav Pediatr*. 2007;28:82–91.
 35. Black MM. Micronutrient deficiencies and cognitive functioning. *J Nutr*. 2003;133(Suppl):S3927–S3931.
 36. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. 2004;158:1113–1115.
 37. Oner O, Alkar IY, Oner P. Relation of ferritin levels with symptoms ratings and cognitive performance in children with attention deficit-hyperactivity disorder. *Pediatr Int*. 2008;50:40–44.
 38. Konofal E, Cortese S. Lead and neuroprotection by iron in ADHD. *Environ Health Perspect*. 2007;115:A398–A399.
 39. Konofal E, Cortese S, Marchand M, Mouren MC, Arnulf I, Lecendreux M. Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children. *Sleep Med*. 2007;8:711–715.
 40. Oner P, Dirik EB, Taner Y, Caykoğlu A, Anlar O. Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. *Tohoku J Exp Med*. 2007;213:269–276.
 41. Sever Y, Ashkenazi A, Tyano S, Weizman A. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. *Neuropsychobiol*. 1997;35:178–180.
 42. Konofal E, Cortese S, Lecendreux M, Arnulf I, Mouren MC. Effectiveness of iron supplementation in a young child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2005;116:e732–e734.
 43. Konofal E, Lecendreux M, Deron J, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. *Pediatr Neurol*. 2008;38:20–26.
 44. Koziellec T, Starobrat-Hermelin B. Assessment of magnesium levels in children with attention deficit hyperactivity disorder (ADHD). *Magnes Res*. 1997;10:143–148.
 45. Starobrat-Hermelin B, Koziellec T. The effects of magnesium physiological supplementation on hyperactivity in children with attention deficit hyperactivity disorder (ADHD). Positive response to magnesium oral loading test. *Magnes Res*. 1997;10:149–156.
 46. Mousain-Bosc M, Roche M, Rapin J, Bali J-P. Magnesium VitB6 intake reduces central nervous system hyperexcitability in children. *J Am Coll Nutr*. 2004;23(Suppl):S545–S548.
 47. Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, Rapin J, Bali J-P. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. *Magnes Res*. 2006;19:46–52.
 48. Salem N Jr, Litman B, Kim H-Y, Gawrisch K. Mechanisms of action of docosahexaenoic acid. *Lipids*. 2001;36:945–959.
 49. Youdim KA, Martin A, Joseph JA. Essential fatty acids and the brain: possible health implications. *Int J Dev Neurosci*. 2000;18:383–399.
 50. Yehuda S, Rabinovitz S, Mostofsky DI. Essential fatty acids are mediators of brain biochemistry and cognitive functions. *J Neurosci Res*. 2000;56:565–570.
 51. Hibbeln J, Ferguson TA, Blasbalg TL. Omega-3 fatty acid deficiencies in neurodevelopment, aggression and autonomic dysregulation. *Int Rev Psychiatry*. 2006;18:107–118.
 52. Chalons S, Vancassel S, Zimmer L, Guilloteau D, Durand G. Polyunsaturated fatty acids and cerebral function: focus on monoaminergic neurotransmission. *Lipids*. 2001;36:937–944.
 53. Chalons S. Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukot Essent Fatty Acids*. 2006;75:259–269.
 54. Colquhoun I, Bunday S. A lack of essential fatty acids as a possible cause of hyperactivity in children. *Med Hypotheses*. 1981;7:673–679.
 55. Burgess JR, Stevens LJ, Zhang W, Peck L. Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *Am J Clin Nutr*. 2000;71:327–330.
 56. Chen J-R, Hsu S-F, Hsu C-D, Hwang L-H, Yang S-C. Dietary patterns and blood fatty acid composition in children with attention-deficit hyperactivity disorder in Taiwan. *J Nutr Biochem*. 2004;15:467–472.
 57. Mitchell EA, Aman MG, Tubott SH, Manku M. Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clin Pediatr*. 1987;26:406–411.
 58. Mitchell EA, Lewis S, Cutler DR. Essential fatty acids and maladjusted behaviour in children. *Prostaglandins, Leukot Med*. 1983;12:281–287.
 59. Stevens LJ, Zentall SS, Deck JL, et al. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *Am J Clin Nutr*. 1995;62:761–768.
 60. Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. A randomised, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr*. 2001;139:189–196.
 61. Stevens LJ, Zhang W, Peck L, et al. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids*. 2003;38:1007–1021.
 62. Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder – a placebo-controlled double-blind study. *Eur J Clin Nutr*. 2004;58:467–473.
 63. Richardson AJ, Puri BK. A randomised double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:233–239.
 64. Richardson AJ, Montgomery P. The Oxford-Durham study: a randomised, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*. 2005;115:1360–1366.
 65. Richardson AJ. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *Int Rev Psychiatry*. 2006;18:155–172.
 66. Sinn N, Bryan J, Wilson C. Cognitive effects of polyunsaturated fatty acids in children with attention deficit hyperactivity disorder symptoms: a randomised controlled trial. *Prostaglandins Leukot Essent Fatty Acids*. 2008;78:311–326.
 67. Ng F, Berk M, Dean O, Bush A. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int J Neuropsychopharmacol*. 2008;21:1–26.
 68. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. *Int J Clin Pharmacol Ther*. 2002;40:158–168.
 69. Fitzpatrick DF, Bing B, Rohdewald P. Endothelium-dependent vascular effects of Pycnogenol. *J Cardiovasc Pharmacol*. 1998;32:509–515.

70. Nishioka K, Hidaka T, Nakamura S, et al. Pycnogenol, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans. *Hypertens Res.* 2007;30:775–780.
71. Greenblatt J. Nutritional supplements in ADHD. *J Am Acad Child Adolesc Psychiatry.* 1999;38:1209–1210.
72. Heimann SW. Pycnogenol for ADHD? *J Am Acad Child Adolesc Psychiatry.* 1999;38:357–358.
73. Tenenbaum S, Paull JC, Sparrow EP, Dodd DK, Green L. An experimental comparison of Pycnogenol and methylphenidate in adults with attention-deficit/hyperactivity disorder (ADHD). 2002;6:49–60.
74. Trebatická J, Kopasová S, Hradečná Z, et al. Treatment of ADHD with French maritime pine bark extract, Pycnogenol. *Eur Child Adolesc Psychiatry.* 2006;15:329–335.
75. Chovanová Z, Muchová J, Sivoňová M, et al. Effect of polyphenolic extract, Pycnogenol, on the level of 8-oxoguanine in children suffering from attention deficit/hyperactivity disorder. *Free Radical Res.* 2006;40:1003–1010.
76. Dvořáková M, Sivoňová M, Trebatická J, et al. The effect of polyphenolic extract from pine bark, Pycnogenol, on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD). *Redox Report.* 2006;11:163–172.
77. Dvořáková M, Ježová D, Blažíček P, et al. Urinary catecholamines in children with attention deficit hyperactivity disorder (ADHD): Modulation by a polyphenolic extract from pine bark (Pycnogenol). *Nutr Neurosci.* 2007;10:151–157.
78. Feingold BF. *Why is Your Child Hyperactive?* 1975, New York: Random House.
79. Swaine A, Soutter V, Loblay R, Truswell AS. Salicylates, oligo-antigenic diets, and behaviour. *Lancet.* 1985;2:41–42.
80. Shaywitz BA, Goldenring JR, Wool RS. The effects of chronic administration of food colorings on activity levels and cognitive performance in developing rat pups treated with 6-hydroxydopamine. *Neurobehav Toxicol.* 1979;1:41–47.
81. Goldenring JR, Batter DK, Shaywitz BA. Sulfanilic acid: behavioural change related to azo food dyes in developing rats. *Neurobehav Toxicol Teratol.* 1982;4:43–49.
82. Kaplita PV, Triggler DJ. Food dyes: behavioural and neurochemical actions. *Trends Pharmacol Sci.* 1982;3:70–71.
83. Kittler FJ, Baldwin DG. The role of allergic factors in the child with minimal brain dysfunction. *Ann Allergy.* 1970;28:203–206.
84. Food and Drug Administration. Food ingredients and packaging. Summary of color additives listed for use in the United States in food, drugs, cosmetics, and medical devices. 2007: Available from: <http://www.cfsan.fda.gov/~dms/opa-col2.html#table1A>. Accessed July 25, 2008.
85. Weiss B. Food additives and environmental chemicals as sources of childhood behavior disorders. *J Am Acad Child Psychiatry.* 1982;21:144–152.
86. Breakey J, Reilly C, Connell H. The role of food additives and chemicals in behavioral, learning, activity, and sleep problems in children. In: Branen AL, Davidson M, Salminen S, Thorngate JH III, eds. *Food Additives*. Second Edition. CRC Press. 2002:87–100.
87. Cormier E. Diet and child behavior problems: fact or fiction? *Pediatr Nurs.* 2007;33:138–143.
88. Arnold LE. Treatment alternatives for attention-deficit/hyperactivity disorder. *J Atten Disord.* 1999;3:30–48.
89. Schab DW, Trinh NH-T. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr.* 2004;25:423–434.
90. McCann D, Barrett A, Cooper A, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet.* 2007;370:1560–1567.
91. Antalis CJ, Stevens LJ, Campbell M, Pazdro R, Ericson K, Burgess JR. Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot Essent Fatty Acids.* 2006;75:299–308.