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Diet in the treatment of ADHD in children—A systematic review of the literature

MAREN JOHANNE HEILSKOV RYTTER, LOUISE BELTOFT BORUP ANDERSEN, TINE HOUMANN, NIELS BILENBERG, ALLAN HVOLBY, CHRISTIAN MØLGAARD, KIM F. MICHAelsen, LOTTE LAURITZEN


Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric conditions in childhood. Dietary changes have been suggested as a way of reducing ADHD symptoms. Aims: To provide an overview of the evidence available on dietary interventions in children with ADHD, a systematic review was carried out of all dietary intervention studies in children with ADHD. Methods: Relevant databases were searched in October 2011, with an update search in March 2013. The studies included describe diet interventions in children with ADHD or equivalent diagnoses measuring possible changes in core ADHD symptoms: inattention, hyperactivity and impulsivity. Results: A total of 52 studies were identified, some investigating whether ADHD symptoms can improve by avoiding certain food elements (20 studies), and some whether certain food elements may reduce ADHD symptoms (32 studies). Conclusion: Elimination diets and fish oil supplementation seem to be the most promising dietary interventions for a reduction in ADHD symptoms in children. However, the studies on both treatments have shortcomings, and more thorough investigations will be necessary to decide whether they are recommendable as part of ADHD treatment.

• ADHD, Dietary intervention, Review.

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequent psychiatric conditions in childhood. It is caused by a combination of genetic and environmental factors, and symptoms vary within and between patients. Not all children with ADHD benefit from the standard pharmaceutical treatment: some experience side-effects, and there is concern about the long-term effects of the drugs on children (1, 2). Dietary changes have therefore been investigated for decades as a way of reducing symptoms in children with ADHD (3) (Fig. 1). The dietary changes that have been suggested as potential treatments of ADHD in children fall into two groups:

1) Dietary interventions that remove elements from the diet, elimination diets;
2) Dietary interventions that increase the intake of certain nutrients.

The removal of elements from the diet (the so-called elimination diets) is based on the idea that some children may have behavioural changes when exposed to certain food items. These intervention studies fall into three categories: artificial food colorants and other additives, sugar, and “Few Foods Diets”.

The research within artificial food colorants and other additives began in the 1970s. It was hypothesized that a diet without natural salicylates and artificial food colorants, the Kaiser Permanente diet, also known as the K-P diet or the Feingold diet, could improve symptoms in children with “hyperactivity” or “minimal brain dysfunction” (4).

A possible effect of sugar and artificial sweeteners has been a focus among parents who report that their children get “hyperactive” after eating a lot of sugar. A few observational studies have found that sugar ingestion was related to ADHD symptoms in children and adolescents...
monoaminergic neurotransmitters, dopamine, serotonin acids, essential fatty acids, vitamins and minerals. The nutrients in focus have been certain amino acids, because of a low intake or because of a higher requirement. ADHD could have deficiencies in these nutrients, either to decrease ADHD symptoms, and dark grey: food elements hypothesized to have a beneficial effect on ADHD symptoms when added to the diet.

Apart from sugar and artificial food colorants, it has been suggested that some children with ADHD could be sensitive to other food items, and that these specific food items vary from child to child (7). Few Foods Diets eliminate all but a few food items from the diet for a period. The diet typically consists of two types of meat, two sources of carbohydrates, two vegetables, two fruits, oil and water (8). Children are identified as “diet sensitive” if they show improvement after a few weeks on this type of diet. If so, food items are re-introduced in a controlled way to identify any specific food causing the child to react. This can be followed by random blinded challenges in which the foods that the child was found to react to were given disguised in other foods or in capsules. The overall idea is to identify the food items to be avoided in each specific case and thus design an individual diet for future use.

The rational for the dietary interventions that increase the intake of certain nutrients are that children with ADHD could have deficiencies in these nutrients, either because of a low intake or because of a higher requirement. The nutrients in focus have been certain amino acids, essential fatty acids, vitamins and minerals.

The interest for amino acids was raised because the monoaminergic neurotransmitters, dopamine, serotonin and norepinephrine, which are involved in the symptoms of ADHD, are synthesized from the amino acid precursors, phenylalanine, tyrosine and tryptophan (9). Thus, it has been suggested that supplements with these amino acids might help children with ADHD. In contrast, concerns have been raised that intake of phenylalanine via the artificial sweetener aspartame could increase symptoms in children with ADHD (10).

The interest in essential fatty acids in relation to ADHD began in 1981 (11), where the first studies focused on supplements of n-6 fatty acids from vegetable oils, but the main focus in this field has been the long-chain n-3 fatty acids (n-3 LCPUFA): docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish oil. The nomenclature indicates the location of the double bond in the carbon chain of the fatty acid, which is preserved during metabolism and is essential for the effects. DHA has been shown to play an important role in the structure and function of the brain (12). Studies in rats have shown that deficiencies in n-3 fatty acids, as well as supplementation with fish oil, affect levels of monoaminergic neurotransmitters (13). Lower blood levels of DHA have been observed in children with ADHD as well as associations between severe ADHD symptoms and low DHA concentrations (14, 15). Maternal fish oil supplementation during lactation has been associated with offspring attention and physical activity both in animal and human studies (16, 17).

When it comes to vitamins, B vitamins, especially B6 (pyridoxine), B9 (folate) and vitamin B12 (cobalamin), are all involved in the synthesis of monoaminergic neurotransmitters as well as in the metabolism of fatty acids (18). Deficiencies may therefore have negative consequences for cognitive functions. Vitamin C has also been used as a supplement in studies on ADHD, presumably based on its anti-oxidative effects, which may protect n-3 LCPUFA or oxidation in the brain in general, or thefact that it improves iron absorption. Carnitine is an ammonium compound with vitamin-like properties, which is provided by the diet or synthesized from lysine and methionine. Carnitine is essential for the transport of fatty acids. Supplementation with carnitine has been found to reduce ADHD-like symptoms in children with fragile X syndrome (19) and it has therefore been suggested that it may have a beneficial effect on children with ADHD.

The minerals zinc, iron and magnesium have all been suggested as potentially relevant supplements to children with ADHD. Zinc is involved in the synthesis of monoaminergic neurotransmitters. Deficiency in these minerals, specifically zinc and iron, is known to cause cognitive impairment in children (20, 21). Observational studies have furthermore found that children with ADHD have a lower status of these minerals (22–24). It has been proposed that children with ADHD may have a
different metabolism of especially zinc, and also that zinc status could modify the effect of factors like fatty acids (25). Iron deficiency has been suggested to be involved in restless legs syndrome (26), which shares some features with ADHD, and it has therefore been hypothesized that iron deficiency could also play a role in ADHD. Moreover, iron status may also influence the metabolism of essential fatty acids (27).

This broad systematic review aims to assess the “state of the art” of all the proposed dietary interventions, in order to qualify recommendations and future research.

Materials and methods
The review was performed in accordance with a predefined but unpublished protocol describing the aim, search strategy, inclusion and exclusion criteria, and the methods used to evaluate the studies.

Strategy of search and selection of literature
Literature search was carried out on 3 October 2011 and updated on 11 March 2013. The databases PubMed, Web of Science, PsycINFO and the Cochrane Library were searched for a combination of relevant words about diet and ADHD (Fig. 2), and the reference lists of the papers

1: “Food” (mesh) OR “diet” (mesh) OR “diet therapy” (mesh) OR “nutrition disorders” (mesh)
2: “micronutrients” (mesh) OR “trace elements” (mesh) OR “zinc” (mesh) OR “Magnesium” (mesh) OR “magnesium deficiency” (mesh) OR “iron” (mesh) OR “iron deficiency anemia” (mesh) OR “copper” (mesh) OR “calcium” (mesh) OR “Niacin” (mesh) OR “vitamin B 12” (mesh) OR “Dietary Supplements” (mesh) OR “vitamin D” (mesh) OR “deficiency” (mesh)
3: “Lipids” (mesh) OR “fatty acids, unsaturated” (mesh) OR “Fatty Acids, essential” (mesh) OR “Fish oils” (mesh) OR “fatty acids” (mesh) OR “carnitine” (mesh)
4: “Milk, Human” (mesh) OR “Breastfeeding” (Mesh)
5: “probiotics” (mesh) OR “candida” (mesh)
6: “Hypersensitivity” (mesh) OR “Allergy and Immunology” (mesh) OR “immunoglobulins” (mesh), “salicylates” (mesh) OR “Milk” (mesh) OR “Glutens” (mesh) OR “Caseins” (mesh)
7: “food additives” (mesh) OR “flavoring agents” (mesh) OR “food preservatives” (mesh) OR “food coloring agents” (mesh) OR “Sweetening agents” (mesh)
8: “Dietary carbohydrates” (mesh)
9: “Amino acids” (mesh)
10: “Ketogenic diet” (mesh)
11: (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
12: “Attention Deficit and Disruptive Behavior Disorder” (mesh) OR “Hyperkinesis” (mesh) OR “Attention Deficit Disorders with Hyperreactivity” (mesh)
13: Search Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English, Danish, All Child: 0-18 years
14: #11 AND #12 AND #13
15: “Food” OR “Diet” OR “nutrition” OR malnutrition
16: “zink” OR “iron” OR “magnesium” OR “copper” OR “Calcium” OR “vitamin” OR micronutrient
17: “fatty acids” OR “EFA” OR “DHA” OR “omega-3” OR “omega-6” OR “carnitine”
18: breastfeeding
19: “Probiotic” OR “candida” OR “microbiota” OR “yeast”
20: “hyperreactivity” OR “allergy” OR “salicylates” OR “Feingold” OR “Kaiser Permanente diet” OR “KP diet” OR “milk” OR “casein” OR “gluten” OR “oligoantgenic diet” OR “oligoallergenic diet” OR “few foods diet” OR “elimination diet”
21: “food additive” OR “food colour” OR “color” OR “flavour” OR “preservative”
22: “sugar” OR “sucrose”
23: “amino acid”
24: “ketogenic diet”
25: (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
26: “ADHD” OR “hyperactivity” OR “inattention” OR “impulsivity” OR “Attention Deficit Hyperactivity Disorder” OR “Minimal Brain Dysfunction”
27: Search Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English, Danish, All Child: 0-18 years
28: #25 AND #26 AND #27
29: Search Limits: published in the last 180 days
30: #25 AND #26 AND #28

Fig. 2. PubMed search strategy for the main search.
restrictions were imposed as to whether the children received medication. Studies with fewer than 10 subjects were excluded.

**Outcomes**

Included studies should report change in core symptoms of ADHD (hyperactivity, impulsivity and inattention) as an outcome, preferably based on validated scales or tests. The scales used were the Conners Scales or the ADHD Rating Scale, but we also accepted studies using locally developed scales, as long as their purpose was to assess ADHD core symptoms. Studies that used tests to assess hyperactivity, impulsivity and inattention were also included. These comprised the Continuous Performance Test (CPT), Matching Familiar Figures Test, Draw-a-Line-Slowly Test, Zero Input Tracking Analyzer and Auxiliary Distraction Task, Freedom from Distractibility Index of the Wechsler Intelligence Scale for Children, among others.

**Results**

A total of 52 studies met the inclusion criteria. The most frequent reasons for excluding studies were that the study included children not diagnosed with ADHD or similar conditions or did not report change in ADHD core symptoms, or had fewer than 10 participants. Due to the heterogeneous nature of the interventions, participants and outcomes, it was decided not to attempt to perform a
meta-analysis, but instead report the data as a systematic review, where we took the size and methodological approach of the studies into account. Others have performed meta-analyses, but heterogeneity was high between studies, making it questionable whether the studies were indeed suitable for pooling (28–31).

The studies fall into two groups: 1) dietary interventions that remove elements from the diet (20 studies) and 2) dietary interventions that increase the intake of certain nutrients (32 studies).

Elimination diets

Artificial food colorants and other additives

The studies assessing the effect of artificial food colorants were either diet studies, assessing whether ADHD symptoms in children improved on a diet without artificial colours (K-P diet), or challenge studies, evaluating whether children’s symptoms worsened when exposed to artificial food colorants (Table 1).

Of the six studies describing the effect of the K-P diet, two were uncontrolled studies (preceding challenge studies) (32, 33) and four had a randomized double-blinded crossover design, in which the children followed a K-P diet and an equally restrictive control diet for 3–4 weeks each (34–37). Four challenge studies assessed the effect of giving artificial food colorants by randomized double-blinded crossover challenges (32, 33, 38, 39). In these studies, children followed a diet without artificial food colorants but were given a cookie every day, which on some days contained artificial food colorants.

Both uncontrolled diet studies reported improved symptoms after the K-P diet, whereas the results of the controlled studies were mixed. None of the diet RCTs found a significant effect that was consistent among parents, teachers and clinical tests, but most did find an effect in the parent’s ratings. Three of the challenge studies found some deterioration in behaviour of the children when exposed to artificial food colorants (32, 33, 38), whereas one study did not find any effect (39). Many of these studies found differences in the effect evaluated by parents and teachers. Overall, the studies do not provide any clear and convincing results.

There are a number of limitations to the studies on artificial food colorants. First, they all had few participants: the largest included 46 children. Besides, all studies but one are more than 30 years old, so children included are likely to differ from the children fulfilling today’s ADHD criteria. Some studies tested a mix of additives, whereas one tested only tartrazine (2 mg). It has, however, been suggested that the realistic daily intake of an American child is up to 150 mg of tartrazine (40), so the study may have overlooked a relevant effect. Finally, all the challenge studies used chocolate cookies as a vehicle for the food colorants. As later and more extensive Few Foods Diets studies have found that some children reacted to cocoa and wheat, this may have blurred any possible effect of the artificial food colorants.

The ambiguous results of the studies and their methodological limitations make it difficult to draw any firm conclusions regarding the effect of artificial food colorants in children with ADHD. However, two large studies carried out on a general population of children (41, 42) both found that normal children showed increase in ADHD-like behaviour after receiving a mix of artificial colorants, so-called “azo-dyes”, together with the preservative sodium benzoate. The reaction was not related to whether the child was known hyperactive or allergic, but seemed linked to genetic polymorphisms in the metabolism of histamine (43). As a result, the European Union has passed a law stating that foods containing “azo-dyes” should bear a warning label stating that they may have adverse effects on children’s behaviour and attention (44).

Four meta-analyses have been carried out on this issue, the most recent published in 2013 (28, 29, 45, 46). All conclude that artificial food colorants have small, but statistically significant adverse effects on ADHD symptoms in some children, but that this is based on studies of limited quality.

Sugar and artificial sweeteners

Five crossover RCTs have assessed the acute effect of sugar and aspartame on children with ADHD or equivalent diagnoses (Table 2). One of the RCTs examined aspartame vs. control (10), one compared sugar and saccharine (47), two compared sugar vs. aspartame (48, 49), and the last tested both sugar and aspartame vs. saccharine (50). Overall, these studies found no change in core ADHD symptoms with either sugar or aspartame; although one found an increase in inattention with sugar relative to both saccharin and aspartame (50).

The studies are relatively old, had few participants and only assessed the effect of short-term exposure. The studies may therefore have missed small effects, effects that only occurred in a minority of children, or after long-term exposure. Furthermore, two of the studies compared two food components with proposed harmful effects (sugar and aspartame), so it may not be possible to evaluate the effect of any of these compounds. At present, the literature does not support the theory that sugar, or any other sweetener, causes symptoms of ADHD in children.

Few foods diets

Seven studies have attempted to test Few Foods Diets in children with ADHD (Table 3); only one of them, however, in a double-blinded RCT design under controlled conditions (51). This study was performed as a crossover study in hospitalized children who received all their food in the Few Foods Diet or a comparison diet from the
Table 1. Studies assessing the effect of artificial food colorants on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis†</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet studies</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kaplan et al., 1989 (37)</td>
<td>RCT crossover</td>
<td>24, 3–6 years, 100% boys, ADD-H (a,c)</td>
<td>Diet with no artificial colorants vs. control for 4 weeks. All food provided</td>
<td>Abbreviated Conners Scales; Motor Accuracy Test of the Southern California Sensory Integration Test; Matching Familiar Figures Test; Memory for Colors test; Visual Attention Span test; Detroit Test of Learning Aptitude; Anima House test from the Wechsler Preschool and Primary Scale of Intelligence</td>
<td>Improvement on diet without artificial food colours (P); No effect (T – only half of the children evaluated); Test: most children not able to complete the tests</td>
</tr>
<tr>
<td>Eich et al., 1979 (36)</td>
<td>RCT crossover</td>
<td>16, age and gender not given, MBD (a)</td>
<td>K-P diet vs. control diet for 4 weeks each</td>
<td>Conners Scales; The Beery Buchtenia Test of Visual Motor Integration; Porteus Maze Test; Digit span subtest of WISC; Quick Neurological Screening test</td>
<td>Diet improved Conners score (P, not T); No improvement in tests</td>
</tr>
<tr>
<td>Harley et al., 1978 (35)</td>
<td>RCT crossover</td>
<td>46, 3–12 years, 100% boys, hyperkinetic reaction of childhood (a,b)</td>
<td>K-P diet vs. control diet for 3 weeks each. All food provided</td>
<td>Conners Scales; Class-room observation; Laboratory observation; WISC; Wide Range Achievement Test Reading; Finger-tapping speed; Kinetic Steadiness; Grooved pegboard</td>
<td>Diet improved Conners scores (P, not T); No improvement in class-room or laboratory observation or in any tests</td>
</tr>
<tr>
<td>Goyette et al., 1978* (33)</td>
<td>Uncontrolled study</td>
<td>16, 4–11 years, gender not given, hyperactive (d)</td>
<td>K-P diet</td>
<td>Conners Scales; Zero Input Tracking Analyzer and Auxiliary Distraction Task</td>
<td>Improvement on Conners Scales (P and T) with diet compared with before diet; Results of tests not reported</td>
</tr>
<tr>
<td>Levy et al., 1978* (32)</td>
<td>Uncontrolled study</td>
<td>22, 4–8 years, 86% boys, hyperactive (a)</td>
<td>K-P diet</td>
<td>Conners Scales; Sprague Ballistographic Chair; CPT; Draw-a-line Slowly test; Motor-Accuracy and Figure-Ground subsets of the Jean Ayres test; Auditory Sequential Memory task from Illinois Test of Psycho-Linguistic Ability; Animal House from Wechsler Preschool and Primary Scale of Intelligence; Mazes subtests from the WISC</td>
<td>Improvement on Conners Scales (P, not T) with diet compared with before diet; No effects on any tests</td>
</tr>
<tr>
<td>Conners et al., 1976 (34)</td>
<td>RCT crossover</td>
<td>15, 6–12 years, gender not given, hyperkinetic reaction of childhood (a)</td>
<td>K-P diet vs. control diet for 4 weeks each</td>
<td>Conners Scales; Clinical Global Impression-Improvement (CGI-I)</td>
<td>Improvement on Conners Scales (P, not T); CGI-I improved more with K-P diet than with placebo diet (psychiatrist)</td>
</tr>
<tr>
<td><strong>Challenge studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams, 1981 (39)</td>
<td>RCT crossover</td>
<td>18, 4–11 years, 83% boys, hyperactive (d)</td>
<td>Mixed colorants (26 mg) (Yellow no. 5, Red no. 3, Red no. 40, Yellow no. 7)</td>
<td>Numerical Memory and Draw-a-Child subtests from McCarthy Scales; Visual-memory sequenced subtest from the Illinois Test of Psycho-linguistic Ability; Peabody Picture Vocabulary Test; “Activity Room” observation; Developmental Test of Visual-motor Integration</td>
<td>No difference with tests (O)</td>
</tr>
<tr>
<td>Williams et al., 1978 (38)</td>
<td>RCT crossover</td>
<td>28, 5–12 years, gender not given, hyperactive (a)</td>
<td>Unspecified mixed colorants (dose not stated) both with and without medicine</td>
<td>Conners Scales</td>
<td>Colorants deteriorated ADHD symptoms on Conners Scales, independent of medicine (P and T)</td>
</tr>
</tbody>
</table>
hospital kitchen. Two open RCTs compared the Few Foods Diet with no treatment (52) or dietary instruction on “healthy food” (53). Four uncontrolled diet studies (8, 54–56) were carried out, of which all but one (54) were followed by double-blinded re-introduction challenges in the children who responded to the initial diet.

The double-blinded crossover RCT found a significant improvement of ADHD symptoms with the Few Foods Diet, and 24% of the children were found to improve during the elimination diet period vs. only 4% in the control period (51). The two open RCTs also found improvement in ADHD symptoms, with response rates of 64–73% (52, 53). The four uncontrolled studies comparing children’s behaviour during the Few Foods Diet period with their behaviour before the introduction of the elimination diet also found a significant decrease in symptoms (8, 54–56). In the three studies that did random blinded challenges, the children had significantly more ADHD symptoms when given suspected foods than when given control food (8, 55, 56). There was no clear pattern in the types of food items causing the reactions.

The studies of Few Foods Diets have serious limitations. First, the apparent effect of the diet in the uncontrolled studies could be explained by factors other than the diet itself (e.g. the beliefs of the parents or the change of home-setting structure that a strict diet warrants). Similarly, the lack of blinding in two of the controlled trials is a potential source of bias. On the other hand, it may be difficult to blind families to a diet that is restrictive and individually tailored to the child’s symptoms (53). Third, most studies included children of parents with a dietary interest (55), and only one study included children referred to a general child psychiatry clinic (51). The latter study was also the only truly blinded RCT, and it had the lowest proportion of responders. In the studies that included a double-blinded challenge phase, only a minority of the children completed the challenges (8, 55), either because they dropped out, or because the food they reacted to was not suitable for double-blinded challenge. The use of such a highly selected study groups limits the relevance of the results of the blinded challenges. Furthermore, a plausible biological explanation for the apparent effect of these diets is lacking, as this does not seem to be explainable by any known allergic mechanism as earlier suggested.

In spite of these limitations, it is intriguing that all seven studies found significant effects on core ADHD symptoms. Beneficial effects were also seen in the studies that included a double-blinded challenge, indicating that this might not just be a placebo effect.

Two recent meta-analyses have analysed the effects of elimination diets. One concluded that restrictive diets may benefit some children with ADHD (28), the effect size being about one third of that of medication, and clinically relevant. However, this meta-analysis also
estimated to last around a year (53) and call for substantial resources from families and the healthcare system. No studies followed the participants longer than 9 weeks, and no studies have assessed the effect of the final individual diet. Furthermore, it is not clear what specific foods the children typically react to, how restrictive the final diets need to be, and whether the nutritional value of this diet is satisfactory.

Increasing intake of certain nutrients

AMINO ACIDS

Three small RCTs (Table 4) have assessed potential effects of supplementation with amino acids (10, 58, 59). The results of these studies did not show any effect of tyrosine or phenylalanine. The study testing tryptophan found an improvement in ADHD symptoms on the parent ratings, but not in the teacher ratings (58). At present, there is no evidence that children with ADHD benefit from amino acid supplementation, but more studies are needed to make firm conclusions.

Table 2. Studies assessing the effect of sugar or aspartame on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis†</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaywitz et al., 1994 (10)</td>
<td>RCT crossover</td>
<td>15, 5–13 years, 73% boys, ADD-H (d)</td>
<td>Aspartame (about 1.3 g*) vs. control (cellulose) for 2 weeks</td>
<td>Conners Scales; Multigrade Inventory scale; Matching Familiar Figures Test; Wisconsin Card Sorting test; the Children’s Checking Task and the Airplane test</td>
<td>No significant difference on Conners Scales (P and T) or tests; Activity subscale at the multigrade Inventory (T) scale significant lower in placebo group</td>
</tr>
<tr>
<td>Wender &amp; Solanto, 1991 (50)</td>
<td>RCT crossover (challenge)</td>
<td>17, 6–8 years, gender not given, ADD-H (a,b)</td>
<td>One sugar drink (35 g) vs. control (aspartame or saccharin)</td>
<td>CPT</td>
<td>Significantly increased inattention in test after sugar intake; No significant difference between the two controls</td>
</tr>
<tr>
<td>Milich &amp; Pelham, 1986 (49)</td>
<td>RCT crossover (challenge)</td>
<td>16, 6–9 years, 100% boys, ADD-H (a,b)</td>
<td>One sugar drink (about 50 mg) vs. control (aspartame)</td>
<td>Conners Scales; Tests developed for occasion</td>
<td>No significant difference on Conners Scales (T) or tests</td>
</tr>
<tr>
<td>Wolraich et al., 1985 (48)</td>
<td>RCT crossover (challenge)</td>
<td>2 × 16, 7–12 years, 100% boys, hyperactive (a,b)</td>
<td>One sugar drink (about 61 mg*) vs. control (aspartame) both fasting and post-prandial</td>
<td>Undefined scales; CPT; Draw a Line Fast test; Draw a Line Slowly test; Match Familiar Figures test; Paired-associate Learning test; Accelerometer output</td>
<td>No significant difference on scales (O), tests or accelerometer output, irrespective of fasting or not</td>
</tr>
<tr>
<td>Gross, 1984 (47)</td>
<td>RCT crossover (challenge)</td>
<td>50, 5–7 years, 72% boys, hyperkinetic syndrome (d)</td>
<td>One sugar drink (75 g) vs. control (saccharin)</td>
<td>Scale made for the occasion rating behaviour</td>
<td>No significant difference (P)</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; P, parents; T, teachers; O, observer; ADD-H, attention deficit disorder with hyperactivity; CPT, Continuous Performance Test.

*Dose calculated based on child’s weight.

†Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

included studies of children who followed diets without food colorants, and thus did not specifically assess the effect of Few Foods Diets. The most recent meta-analysis found that a large effect size in all included studies was reduced to an insignificant effect when looking only at assessments made by an independent blinded assessor (29).

Few Foods Diets may, however, even despite a significant effect, not be relevant in ordinary treatment. None of the studies assessed how well children accepted the diet. Following a diet is often described as laborious and disruptive to social life, and adherence is often poor (57). A restricted Few Foods Diet for a long period can become nutritionally inadequate, especially in growing children, and requires supervision by professionals (52). Few Foods Diets are not meant as treatment, but only as a method to identify diet-sensitive children. The actual treatment is the individually tailored diet designed after repeated challenges have identified which food items should be avoided. The entire reintroduction process is
Overall, the plant oil interventions did not find any convincing beneficial effects on ADHD symptoms. One uncontrolled study supplementing with 400 mg/day of ALA for 3 months found a reduction in total hyperactivity score on parent rating scales, relative to before the intervention (74). However, a RCT (75) found no effect after 7 weeks of supplementation with 120 mg/day of ALA and 480 mg/day of LA. Only one small study (73) examined the effect of exclusive supplementation with n-6 fatty acids and did not find any effect.

**Table 3. Studies assessing Few Foods Diets in children with attention-deficit/hyperactivity disorder (ADHD).**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelsser et al., 2011</td>
<td>Open RCT</td>
<td>100, 4–8 years, 86%</td>
<td>5-week elimination diet vs. instructions on healthy diet</td>
<td>Conners and the ADHD rating scales</td>
<td>Significantly fewer symptoms with elimination diet on Conners and the ADHD rating scales (T and P); Improvement for 64% of children</td>
</tr>
<tr>
<td>Pelsser, Frankena, et al., 2009</td>
<td>Open RCT</td>
<td>27, 4–9 years, 81%</td>
<td>5-week elimination diet vs. waiting list</td>
<td>Conners and the ADHD rating scales</td>
<td>Significantly fewer symptoms with elimination diet on Conners and the ADHD rating scales (P and T); Improvement for 73% of children</td>
</tr>
<tr>
<td>Schmidt et al., 1997</td>
<td>RCT crossover</td>
<td>49, 6–12 years, 96%</td>
<td>9-week elimination diet vs. control diet</td>
<td>Conners Scales; CPT and PALT tests</td>
<td>Significantly fewer symptoms with elimination diet on Conners Scales (O, not T) or CPT and PALT tests; Improvement for 25% of children</td>
</tr>
<tr>
<td>Boris &amp; Mandel, 1994</td>
<td>Uncontrolled diet+ blind crossover challenge</td>
<td>26, 3–12 years, 73%</td>
<td>2-week diet → open challenge → blind random challenge</td>
<td>Conners Scales</td>
<td>Improvement with diet for 73% of children on Conners Scales (P); Significantly more symptoms with suspected foods in blind challenge</td>
</tr>
<tr>
<td>Carter et al., 1993</td>
<td>Uncontrolled diet+ blind crossover; Challenge</td>
<td>78, 3–12 years, 88%</td>
<td>3-week diet → open challenge → blind random challenge</td>
<td>Conners Scales; PALT and MFF test.</td>
<td>Improvement with diet for 76% of children on Conners Scales (P); Significantly more symptoms with suspected foods (P and O) and improved PALT and MFF test. test results</td>
</tr>
<tr>
<td>Egger et al., 1985</td>
<td>Uncontrolled diet+ blind crossover challenge</td>
<td>76, 2–15 years, gender not given, hyperkinetic syndrome or overactivity behavioural disturbance</td>
<td>3-week diet → open challenge → blind random challenge</td>
<td>Conners Scales; Porteus maze test and MFF, accelerometer</td>
<td>Improvement with diet for 82% of children (P and O); Significantly more symptoms with suspected foods on Conners Scales (P and O) and Porteus maze test and MFF tests, but no change in accelerometer</td>
</tr>
<tr>
<td>Rapp, 1978</td>
<td>Uncontrolled diet</td>
<td>24, 5–16 years, gender not given, hyperactive</td>
<td>1-week diet → open challenge</td>
<td>GCI</td>
<td>Improvement on diet for 50% of children on GCI (P)</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; P, parents; T, teachers; O, observer; GCI, Global Clinical Impression; PALT, Paired Associate Learning Test; MFF, Matching Familiar Figures Test; CPT, Continuous Performance Test; GCI, Global Clinical Impression.

*Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

**Essential fatty acids**

We identified 16 studies investigating the effect of essential fatty acids supplementation on ADHD symptoms in children. Thirteen of these studies supplemented with fish oils containing n-3 LCPUFA (DHA and EPA) (60–72). Three studies used plant oil supplements providing linoleic acid (LA) and alpha-linolenic acid (ALA) (73–75) (Table 5). Six of the studies giving fish oil also supplemented with n-6 fatty acids, usually gamma-linolenic acid (GLA).
In the fish oil supplementation trials, one of the two uncontrolled studies found a reduction in ADHD symptoms (64). However, the results from the 11 controlled RCTs are more ambiguous. One of the RCTs reported a significant difference in an overall ADHD symptom scale between the intervention and the control group (72), while the remaining 10 studies did not find any overall effect. However, three of them (62, 68, 69) did find a positive effect on one or more of the ADHD subscales, although not on the same subscales in all studies, and one (65) found a positive effect on the CPT.

The fish oil RCTs have four major limitations: frequent use of multiple testing, a relatively low number of participants, low doses of n-3 LCPUFA, and relatively short intervention periods. Multiple testing using many evaluation scales is seen because n-3 LCPUFA may affect ADHD symptom areas differently, but without correction for multiple testing it increases the risk of chance findings. Only four of the fish oil RCTs had 90 participants (68–70, 72) and detecting a possible effect of fish oil on ADHD symptoms may require the power of an even larger number of participants. Most of the studies have used lower doses than those generally used in fish oil research (typically 1–3 g/day of n-3 LCPUFA) (76). Only two of the RCTs gave >1 g/day of n-3 LCPUFA (66, 70), and five gave 0.5–1 g/day of n-3 LCPUFA (62, 63, 67, 68, 72). The interventions had a duration from 4 to 26 weeks, and six of the studies lasted 15 weeks (60–62, 68–70, 72). Assuming that fish oil affects ADHD symptoms by incorporation into the brain, it may be expected to take some time before any effect occurs. The study showing an effect on overall ADHD-scale scores (72) and one of the studies with subscale effects (68) were among the four studies that had 90 participants, gave 500 mg/day of n-3 LCPUFA and lasted 15 weeks.

Most of the fish oil RCTs used plant oil as control (63, 65–68, 70, 72), and as mentioned above these oils have been used as the primary intervention in other studies (73–75). This seems contradictory, but as the plant oils are used in low doses and furthermore have not been shown to affect ADHD symptoms, this is not expected to blur the possible effect of fish oil. One study have used fish oil supplementation in combination with other fatty acids, vitamins and minerals (61) and caution should be taken to interpret these results together with the studies only intervening with fish oil. Three studies allowed participant to be on ADHD medication (62, 63) or gave fish oil as an adjunct to medication (60).

Overall, the evidence for a reduction in ADHD symptoms following supplementation with essential fatty acids from plant oils is sparse and showed no clear improvements in ADHD symptoms. Biologically, it is more plausible that supplementation with n-3 LCPUFA could

Table 4. Studies assessing the effect of amino acids on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>N, age, sex, diagnosis†</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaywitz et al., 1994 (10)</td>
<td>RCT crossover</td>
<td>15, 5–13 years, 73% boys, ADD (a)</td>
<td>Phenylalanine (as aspartame) 300 mg vs. control (cellulose) for 2 weeks</td>
<td>Conners and Multigrade Inventory scales; Matching Familiar Figur Test, Wisconsin Card Sorting test, the Children’s Checking Task and the Airplane tests</td>
<td>No significant difference on Conners and multigrade Inventory scales (P or T) or the Matching Familiar Figur Test, Wisconsin Card Sorting test, the Children’s Checking Task and the Airplane tests</td>
</tr>
<tr>
<td>Zametkin et al., 1987 (59)</td>
<td>RCT crossover</td>
<td>11, 6–12 years, 100% boys, ADD-H (a)</td>
<td>Phenylalanine, 400–700 mg* vs. control tablets for 2 weeks</td>
<td>Conners Scales; CGI, CPT</td>
<td>No significant difference on Conners Scales (P) or CGI and CPT tests</td>
</tr>
<tr>
<td>Nemzer et al., 1986 (58)</td>
<td>RCT crossover</td>
<td>14, 7–12 years, 79% boys, ADD (a,b)</td>
<td>Tyrosine, 4.2 g or tryptophan, 3 g* vs. control (lactose) each for 1 week</td>
<td>Conners Scales and, David’s Hyperkinetic Scale; WISC-R</td>
<td>No significant difference on Conners Scales and, David’s Hyperkinetic Scale with tyrosine (P and T) or WISC-R Subtest of Concentration and Impulsivity; Significant improvement on Conners Scales and, David’s Hyperkinetic Scale with tryptophan (P, not T), but not in test</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; P, parents; T, teachers; O, observer; ADD-H, attention deficit disorder; ADD-H, attention deficit disorder with hyperactivity, Swanson, Nolan and Pelham rating; CPT, Continuous Performance Test; CGI, Clinical Global Impression scale; WISC-R, Wechsler Intelligence Scale for Children—Revised.

*Dose calculated based on child’s weight.
†Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.
Table 5. Studies assessing the effect of essential fatty acids (fish oil in the top and plant oils in the bottom) on children with attention-deficit/hyperactivity disorder (ADHD).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perera et al., 2012 (72)</td>
<td>RCT</td>
<td>98, 6–12 years, 73%</td>
<td>Fish oil and evening primrose oil <em>(593 mg n-3 PUFAs + 362 mg n-6 PUFAs)</em> vs.</td>
<td>Non-standardized scale</td>
<td>Fish and evening primrose oil significantly improved a non-standardized scale scores (P); Further improvement from 3 to 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD (a)</td>
<td>control (sunflower oil) for 26 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milte et al., 2012 (70)</td>
<td>RCT</td>
<td>90, 7–12 years, 80%</td>
<td>EPA, 1109 mg + DHA, 108 mg or EPA, 264 mg + DHA, 1032 mg vs. control (safflower oil) for 16 weeks</td>
<td>Conners Scales</td>
<td>No significant difference on Conners Scales (P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD (a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assareh et al., 2012 (71)</td>
<td>RCT</td>
<td>40, 6–12 years, 75%</td>
<td>DHA, 241 mg + EPA, 33 mg + n-6 PUFAs, 180 mg vs. control (not given) for 10 weeks</td>
<td>ADHD Rating Scale</td>
<td>No significant difference on scales or subscales (P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD (a)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Manor et al., 2012 (69)</td>
<td>RCT</td>
<td>200, 6–13 years, 67%</td>
<td>DHA, 40 mg + EPA, 80 mg vs. control (cellulose) for 15 weeks, followed by 15 weeks DHA + EPA to all</td>
<td>Conners Scales</td>
<td>No significant overall difference, but significant improvement on 1 (restless/impulsive) of 8 Conners subscales (P, not T) and on 6 of 16 Conners subscales for subgroup with most symptoms; Uncontrolled part: Improvement on 2 of 8 Conners subscales (T) and on 3 of 8 (P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD (a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gustafsson et al., 2010 (68)</td>
<td>RCT</td>
<td>109, 7–12 years, mostly</td>
<td>DHA, 2.7 mg + EPA, 500 mg vs. control (rapeseed oil and MCFA) for 15 weeks</td>
<td>Conners Scales</td>
<td>No significant overall difference, but significant improvement on 1 (inattention) of 3 Conners subscales (T, not P) and significant improvement on overall Conners Scales score for subgroup with ADHD and conduct disorder (T, not P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD combined type (a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson et al., 2009 (67)</td>
<td>RCT</td>
<td>75, 8–18 years, 85%</td>
<td>DHA, 174 mg + EPA, 558 mg + GLA, 60 mg vs. control (olive oil) for 12 weeks, followed by 12 weeks of DHA, EPA + GLA to all</td>
<td>ADHD rating scale; GCI</td>
<td>No overall significant difference on ADHD rating scale scores (P), but significant improvement on GCI; &gt; 25% improvement for 26% of intervention children and 7% of control children Uncontrolled part: No difference between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD(combined/ inattentive type) (a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bélanger et al., 2009 (66)</td>
<td>RCT</td>
<td>37, 6–11 years, 69%</td>
<td>DHA, 300 mg + EPA, 730 mg* vs. control (sunflower oil) for 8 weeks, followed by 8 weeks of DHA + EPA to all</td>
<td>Conners Scales; SWAN scale; CPT</td>
<td>No significant difference on Conners and SWAN scales in RCT (P and T) or CPT; Uncontrolled part: No further improvement in intervention group, but improvement on 1 of 14 Conners subscales in former control group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD (a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaisman et al., 2008 (65)</td>
<td>RCT</td>
<td>83, 8–13 years, 75%</td>
<td>DHA, 125 mg + EPA, 125 mg vs. control (rapeseed oil) for 12 weeks</td>
<td>Conners Scales; CPT</td>
<td>No significant difference on Conners Scales (P), but improvement in CPT tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boys, ADHD (a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germano et al., 2007 (64)</td>
<td>Uncontrolled</td>
<td>31, 8 years on avg., 90% boys ADHD (a)</td>
<td>DHA, 0.9 g + EPA, 1.7 g* for 8 weeks</td>
<td>Conners Scale</td>
<td>Significant improvement in hyperactivity and inattention on Conners Scale (P)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirayama et al., 2004 (63)</td>
<td>RCT</td>
<td>40, 6–12 years, 80% boys, ADHD (a)</td>
<td>Soya milk and bread with DHA, 514 mg + EPA, 100 mg vs. control (olive oil) for 8 weeks</td>
<td>DSM-IV questionnaire scales; Developmental test of visual–motor integration Impatience test and memory test; CPT and Development Test of Visual Perception</td>
<td>No significant difference on DSM-IV questionnaire scales (P and T) and Developmental test of visual–motor integration Impatience test or memory test, but significant improvement in CPT and Development Test of Visual Perception, tests in control group compared with fish oil group</td>
</tr>
<tr>
<td>Stevens et al., 2003 (62)</td>
<td>RCT</td>
<td>50, 6–13 years, ~88% boys, ADHD (a) + Essential fatty acid deficiency.</td>
<td>DHA, 480 mg + EPA, 80 mg + AA, 40 mg + GLA, 96 mg vs. control (olive oil) for 16 weeks</td>
<td>Conners and DBD scales; CPT and Woodcock-Johnson Psycho-Educational Battery-Revised test</td>
<td>No significant difference on Conners and DBD scales, but significant improvement in 2 (conduct and attention) of 10 DBD subscales (P and T) and improvement in 1 (reaction time) of 7 CPT and Woodcock-Johnson Psycho-Educational Battery-Revised test parameters; Improvement in ADHD symptoms at the highest level of n-3 LCPUFA in the blood</td>
</tr>
<tr>
<td>Harding et al., 2003 (61)</td>
<td>Open uncontrolled</td>
<td>20, 7–12 years, gender not given AD/HD (a)</td>
<td>Mixed supplement with DHA, 120 mg + EPA, 180 mg + GLA, 45 mg or methylphenidate (duration not given)</td>
<td>CPT</td>
<td>Improvement after supplement not stated; No significant difference between diet and medicine group in CPT tests;</td>
</tr>
<tr>
<td>Voigt et al., 2001 (60)</td>
<td>RCT</td>
<td>63, 6–12 years, mostly boys, ADHD (a)</td>
<td>DHA, 345 mg vs. control (not given) for 16 weeks</td>
<td>Conners and CBCL scales; TOVA and Children’s Color Trails tests</td>
<td>No significant difference on Conners and CBCL scales (P) or TOVA and Children’s Color Trails tests</td>
</tr>
<tr>
<td>Raz et al., 2009 (75)</td>
<td>RCT</td>
<td>63, 7–13 years, 60% boys, ADHD (a)</td>
<td>ALA, 120 mg + LA, 480 mg vs. control (vitamin C) for 7 weeks</td>
<td>DSM-IV questionnaire for ADHD and Conners Scales; TOVA tests</td>
<td>No significant difference on DSM-IV questionnaire for ADHD and Conners Scales (P and T) or TOVA tests</td>
</tr>
<tr>
<td>Joshi et al., 2006 (74)</td>
<td>Uncontrolled</td>
<td>30, 7 years on avg., 73% boys ADHD (a,b)</td>
<td>ALA, 400 mg for 12 weeks</td>
<td>ADHD rating scale</td>
<td>Significant improvement on all tested ADHD rating scales (P)</td>
</tr>
<tr>
<td>Arnold et al., 1989 (73)</td>
<td>RCT crossover</td>
<td>18, 6–12 years, 100% boys, ADHD (a,b)</td>
<td>LA, 2.8 g + GLA, 320 mg vs. control (paraffin) for 4 weeks</td>
<td>Conners Scale</td>
<td>No significant difference on Conners Scales but significant improvement on hyperactive subscale (T, not P)</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; ALA, alpha-linolenic acid; LA, linoleic acid; GCI, Global Clinical Impression; P, parents; T, teachers; O, observer; SWAN, Strengths and Weaknesses in ADHD and Normal Behaviors; DBD, Disruptive Behavior Disorders Rating Scale; TOVA, Test of Variables of Attention; CBCL, Child Behavior Checklist; CPT, Continuous Performance Test; CGI, Clinical Global Impression scale.

*Dose calculated based on child’s weight.

†Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.
By contrast, a Cochrane review concluded that there is little evidence that LCPUFA supplementation provides any benefit for the symptoms of ADHD in children and adolescents (31). A fourth meta-analysis calculated that, to show an effect, a study needs 330 participants and none of the current studies can match this (30).

**VITAMINS**

Seven studies (Table 6) investigated whether children with ADHD could benefit from vitamin supplementation. However, none of these studies investigated the use of multi-vitamin supplements in doses in line with the Recommended Daily Allowances (RDA), but all supplied

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis†</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbasi et al., 2011 (82)</td>
<td>RCT</td>
<td>40, 7–13 years, 70% boys, ADHD (a)</td>
<td>Acetyl-L-carnitine, 1–3 g vs. methylphenidate for 6 weeks</td>
<td>ADHD rating scales</td>
<td>No significant difference on ADHD rating scales (P and T), but possibly fewer side-effects of methylphenidate</td>
</tr>
<tr>
<td>Arnold et al., 2007 (81)</td>
<td>RCT</td>
<td>112, 5–12 years, 74% boys, ADHD (a)</td>
<td>Acetyl-L-carnitine, 1–3 g vs. “identical soluble powder” for 16 weeks</td>
<td>Conners and CGI scales</td>
<td>No significant difference on Conners and CGI scales (P and T)</td>
</tr>
<tr>
<td>Harding et al., 2003 (61)</td>
<td>Open uncontrolled</td>
<td>20, 7–12 years, gender not given, ADHD (a)</td>
<td>Mix of various mega-doses vitamins + fish oil, amino acids, probiotics vs. methylphenidate (duration not given)</td>
<td>CPT</td>
<td>No significant difference between treatments on CPT tests</td>
</tr>
<tr>
<td>Van Oudheusden &amp; Scholte, 2002 (80)</td>
<td>RCT crossover</td>
<td>26, 6–13 years, 100% boys, ADHD (a)</td>
<td>L-Carnitine, 3 g vs. identically looking and tasting drink for 8 × 3 weeks</td>
<td>Conners and CBCL scales</td>
<td>Significant improvement on Conners and CBCL scales (T and P)</td>
</tr>
<tr>
<td>Haslam et al., 1984 (79)</td>
<td>Uncontrolled† RCT crossover</td>
<td>41 (7 in RCT), 7–11 years, both boys and girls (gender-ratio not given), ADD (a,b)</td>
<td>3-month open-phase with increasing doses of vitamin for all Followed by RCT with mega-doses vitamin B3, B5, B6, C vs. placebo capsule for 6 weeks.</td>
<td>Conners Scale</td>
<td>No significant difference on Conners Scales (P, T and O)</td>
</tr>
<tr>
<td>Brenner, 1982 (78)</td>
<td>RCT crossover</td>
<td>100, 4–15 years, gender not given, MBD (a)</td>
<td>Mega-dose vitamin B1, B5, B6 or control (lactose) for 3 days each</td>
<td>No scales used</td>
<td>Tendency towards improvement on days with one of the vitamins (mostly to vit. B5) (no statistical testing)</td>
</tr>
<tr>
<td>Arnold et al., 1978 (77)</td>
<td>RCT</td>
<td>31, 5–12 years, 74% boys, MBD (a,b)</td>
<td>Mega-dose vitamin B3, B5, B6, C and glutamate vs. similar tasting placebo powder for 2 weeks</td>
<td>Conners Scales and David’s Hyperkinetic Rating Scale</td>
<td>No significant difference on Conners Scales and David’s Hyperkinetic Rating Scale, (P and T)</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; RDA, Recommended Daily Allowance; P, parents; T, teachers; O, observer; ADD-H, attention deficit disorder with hyperactivity; MBD, minimal brain dysfunction; CPT, Continuous Performance Test; CGI, Clinical Global Impression scale; CBCL, Clinical Behavior Checklist.

†Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.
specific vitamins in “mega-doses”, many times above RDA (61, 77–79). One non-randomized (61) and one controlled study (78), which supplied mega-doses of different vitamins, reported an effect, but these studies have severe methodological limitations, such as lack of randomization, extremely short intervention periods and lack of statistical testing. Two more well-designed RCTs testing mega-doses of combinations of vitamins B3, B5, B6 and C, did not find any effect (77, 79). One of them reported deterioration in some ADHD symptoms after vitamin supplementation, and nearly half of the children developed elevated levels of liver enzymes when taking the vitamins, suggesting that the supplements may have a harmful effect (79). One small RCT found a positive effect of carnitine supplementation (80), but two larger RCTs did not find any effect (81, 82), although one did suggest a benefit to children with the inattentive subtype of ADHD (81).

Overall, there is no evidence that mega-dose vitamin supplementation ameliorate symptoms in children with ADHD. Moreover, studies indicate that megadoses of vitamins B3, B5, B6 and C combined may be liver toxic and should be discouraged.

MINERALS

We identified seven studies (Table 7) investigating the effect of mineral supplementation in children with ADHD: three RCTs focusing on zinc (83–85), two on iron (86, 87), and two on magnesium (88, 89). Two of the three double-blind RCTs of the effect of zinc supplementation found a significant positive effect on ADHD symptoms (83, 84), and one of them found that children with the lowest blood concentration of zinc and essential fatty acids benefited the most from the supplement. However, this study was limited by a high dropout rate, and the supplied dose of zinc (150 mg/day) was so high that it may have caused side-effects (84). The last study used a lower dose of zinc, which was increased halfway through the study (85). Although this did not result in any effect on ADHD symptoms, the group receiving zinc required a lower dose of central stimulating drugs (85). The two studies reporting an effect were carried out in Iran and Turkey, whereas the study that did not find any effect was from the USA where the prevalence of zinc deficiency may be lower.

In the studies with iron supplementation, a significant effect was only observed in a small uncontrolled intervention (86), whereas no effect on ADHD symptoms was found in the RCT, although a tendency towards improvement was found measured by Clinical Global Impression (87). This RCT was rather small and included children without anaemia, but with low iron stores (s-ferritin < 30 mg/kg). Two studies with magnesium supplementation (88, 89) both reported improvement in ADHD symptoms, but both have severe methodological problems, such as lack of randomization, and ADHD symptoms were not assessed by any known rating scale.

Based on these studies, there is no evidence to recommend zinc, iron or magnesium supplements to children with ADHD, but supplementation with zinc could be considered in areas with a high prevalence of zinc deficiency.

Conclusion

For most of the interventions regarding dietary components in children with ADHD, only few studies have been conducted, most with few participants and with a number of methodological flaws. These include problems concerning whether the rater was truly blinded (a parent involved in delivering the intervention may not be truly blinded), and old studies with uncertainty regarding the diagnostic classification as well as the psychometric qualities of the outcome measures used. Most studies did not mention whether the effect of dietary treatment depended on age, although a few studies found that artificial food colours had a more pronounced effect in the youngest (pre-school) children (32, 33). Thus, for most dietary interventions there is not enough evidence to recommend their routine use in clinical practice. There is some evidence that certain artificial food colorants may affect behaviour in children, but this effect is apparently not specific for children with ADHD. A few studies suggest that children with ADHD and sub-clinical deficiencies of zinc may benefit from supplementation.

Two types of interventions, Few Foods Diets and fish oil supplementation, seem to hold some promises with respect to reducing ADHD symptoms, but both need more thorough investigation before recommendations can be made. Few Foods Diets appear to have a consistently positive effect in the short-term in some children with ADHD. It is, however, not meant as a long-term treatment, but a diagnostic tool to identify children who are sensitive to certain foods. It is unknown what characterizes the types of food components that are problematic and few studies have assessed the effect of subsequent food challenges for more than a few weeks, and no studies have described the effect of the final diet. Several properly randomized and controlled trials have investigated the effect of fish oil supplementation, but the results are currently inconclusive with respect to the overall efficacy on ADHD symptoms. This may be explained by the low doses used in the studies, short intervention duration and lack of power. Meta-analysis of the fish oil RCTs tend to show some evidence for a small to modest effect and there are plausible biological mechanisms. Furthermore, fish oil-supplementation offers minimal inconvenience and no major side-effects.

Dietary alternatives in the treatment of ADHD patients are welcome, as the current pharmacological treatment is
Table 7. Studies assessing the effect of minerals on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>n, age, sex, diagnosis&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Results (rater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold et al., 2011 (85)</td>
<td>RCT</td>
<td>52, 6–14 years, 84% boys, ADHD (a)</td>
<td>Zinc glycinate, 15–30 mg vs. control (not given) for 13 weeks (8 weeks without and 5 weeks with d-amphetamine)</td>
<td>Conners and SNAP-IV scales; MMF, CPT and Seat Activity tests</td>
<td>No significant difference on Conners and SNAP-IV scales (P and T) or MMF, CPT and Seat Activity tests</td>
</tr>
<tr>
<td>Konofal et al., 2008 (87)</td>
<td>RCT</td>
<td>23, 5–8 years, 77% boys, ADHD (a)+ Non-anemic Ferritin &lt; 30 ng/ml</td>
<td>Iron, 80 mg vs. identical tablets for 12 weeks</td>
<td>Conners and ADHD rating scales; GCI</td>
<td>No significant difference on Conners and ADHD rating scales (P and T), but significant effect on GCI; General improvement</td>
</tr>
<tr>
<td>Mousain-Bosc et al., 2006 (89)</td>
<td>Uncontrolled</td>
<td>40, 0–15 years, gender not given ADHD (a)</td>
<td>Magnesium, 180 mg + vit. B6, 18 mg for 0–6 months</td>
<td>No scales used</td>
<td></td>
</tr>
<tr>
<td>Akhondzadeh et al., 2004 (83)</td>
<td>RCT</td>
<td>44, 5–11 years, 60% boys, ADHD (a)</td>
<td>Zinc sulphate, 55 mg vs. control (sucrose) for 6 weeks</td>
<td>ADHD rating scales</td>
<td>Significant beneficial effect of zinc on ADHD rating scales (P and T)</td>
</tr>
<tr>
<td>Bilici et al., 2004 (84)</td>
<td>RCT</td>
<td>400, 6–14 years, gender not given ADHD (c)</td>
<td>Zinc sulphate, 150 mg vs. control (sucrose) for 12 weeks</td>
<td>Conners, DuPaul Parent Ratings of ADHD and occasional developed scales</td>
<td>Significant beneficial effect of zinc on Conners, DuPaul Parent Ratings of ADHD and occasional developed scales (P and T)</td>
</tr>
<tr>
<td>Sever et al., 1997 (86)</td>
<td>Uncontrolled</td>
<td>14, 7–11 years, 100% boys, ADHD (a), Non-iron-deficient</td>
<td>Iron, 150 mg* for 1 month</td>
<td>Conners Scales</td>
<td>Significant improvement on Conners Scales (P, not T)</td>
</tr>
<tr>
<td>Starobrat-Hermelin &amp; Kozielec, 1997 (88)</td>
<td>Open, non-randomized controlled</td>
<td>75, 7–12 years, gender not given, ADHD (a)</td>
<td>Magnesium, 200 mg vs. “standard treatment” for 6 months</td>
<td>Conners Scales and Wender’s Scale of Behavior and the Quotient of Development to Freedom from Distractibility</td>
<td>Significant effect of magnesium on Conners Scales and Wender’s Scale of Behavior and the Quotient of Development to Freedom from Distractibility (P and T)</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; GCI, Global Clinical Impression; P, parents; T, teachers; O, observer; SNAP-IV scale, Swanson, Nolan and Pelham rating scale; MMF, Matching Familiar Figures Test; CPT, Continuous Performance Test.

*Dose calculated based on child’s weight.

<sup>†</sup>Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.
inefficient in some children with ADHD and may have problematic side-effects. It therefore seems worthwhile to continue research on diet, specifically to examine the long-term effect of restricted diets in sensitive children and to perform a sufficiently powered long-term trial with an appropriate dose of fish oil.

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