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Diet in the treatment of ADHD

A systematic review of the literature

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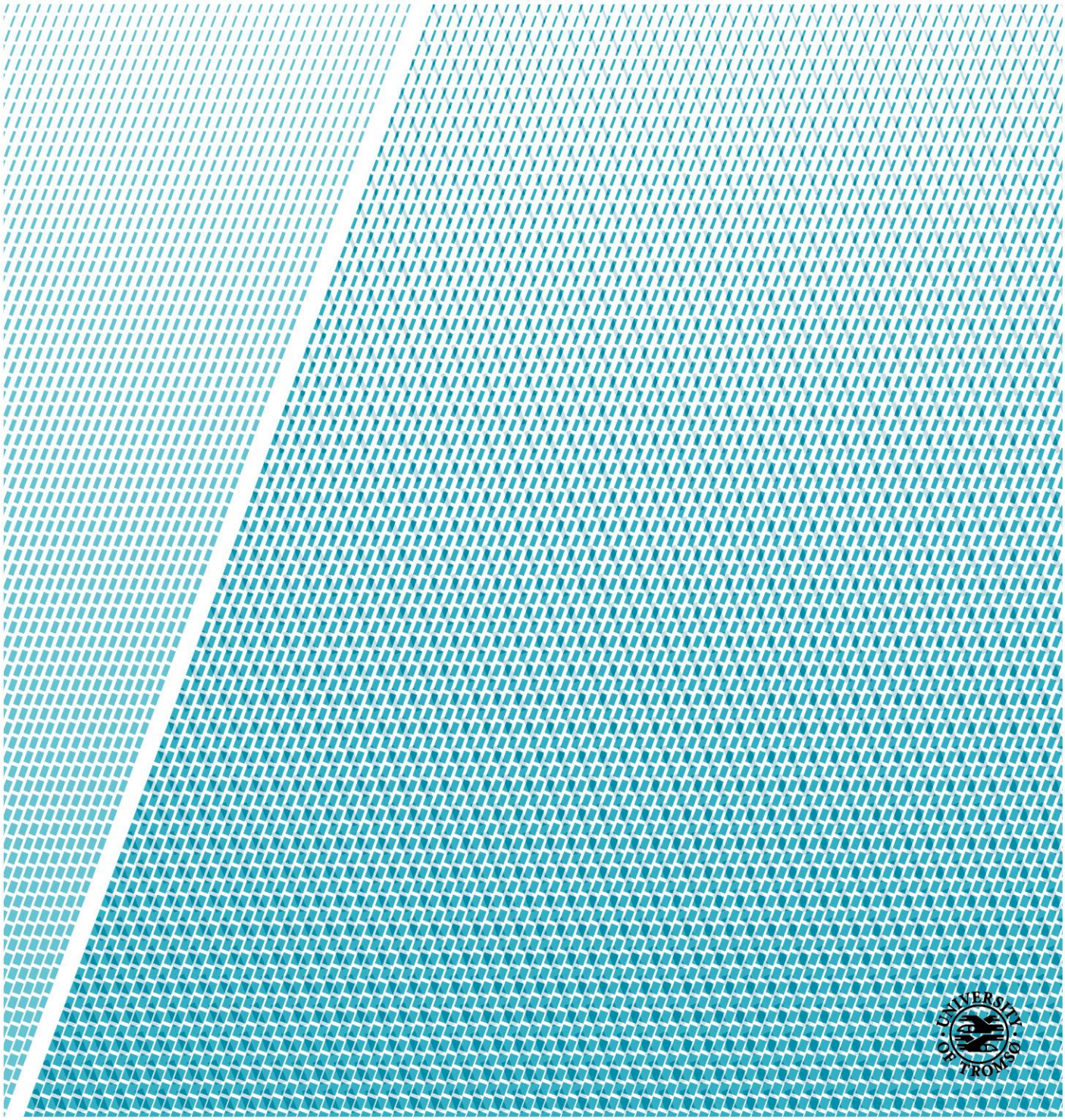

Foreword

This thesis aimd to investigate the evidence up to date for diet as the treatment for ADHD. In order to do this several articles on different nutritional supplements, as well as whole diets, were reviewed.

I have a special interest in the gut microbiota, sickness as consequence of Western lifestyle, and paediatrics. Therefore, I choose children with ADHD and diet as topic for this thesis. I contacted professor Eyvind J. Paulssen, at the Department of Clinical Medicine at UiT The Arctic University of Tromsø, who I remembered for his lectures about gut-health and also for punctilious training in journal writing, and asked for his mentoring. I also got guidance on ADHD in children by Dr. Judeson Joseph, lecturer in Child and Adolescent Mental Health at the Department of Clinical Medicine.

I would like to address a special thanks to my supervisor, professor Eyvind J. Paulssen. Thanks for the follow-up through these years, for the good advice and all the feedback and help. Also thanks to Dr. Judeson Joseph for helping with the clinical perspective.

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Martine Teres Apelqvist Ekhorn

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1 Abstract

Background: Attention deficit hyperactivity disorder, ADHD, is estimated to be the most common behavioural disorder in children, affecting 6-12% of children worldwide (1). The condition has only a few options for evidence-based treatment (2), and public accessible numbers from The prescription register of the Norwegian National Institute of Public Health have shown more than a threefold increase in the use of medication for ADHD since 2004 (3). Studies have shown an association between ADHD and western dietary pattern (4), and there seems to be an increasing interest in whether diet influences the symptoms or not.

Objectives: This study aims to collect the most recent studies, and their results, on diet as the treatment for ADHD, to determine if there is any conclusive data that can be clinically used today.

Methods: The study is an evaluation of published literature, selected through a defined search strategy in PubMed, U.S National Library of Medicine National Institutes of Health.

Results: A total of 21 articles met the inclusion criteria, some investigating the effect of dietary supplements and some investigating the effect of whole diets.

Discussion: The result of this study does not give a defined answer around diet as the treatment for ADHD, nevertheless it points out some interesting findings for further investigation.

Conclusions: Despite compelling evidence for Omega-3 polyunsaturated fatty acids as a treatment for ADHD, the effects of other nutritional supplements are not negligible and suggest not only specific nutrient but whole diets as treatment options for ADHD.

2 Introduction

Attention deficit hyperactivity disorder, ADHD, is estimated to be the most common behavioural disorder in children, affecting 6-12% of children worldwide. The International Classifications of Diseases 10th edition, ICD-10, describes ADHD as consisting of three main symptoms, inattention, hyperactivity and impulsivity, that must be present for more than six months and manifest before the age of seven (1).

The prevalence of ADHD in the Norwegian population is assumed to be 3-5%, where the male-to-female sex ratio is 4:1. The difference between the sexes is explained as a general higher activity level in boys, and that the main symptom in girls is inattention, and therefore harder to discover (5).

Public accessible numbers from The prescription register of the Norwegian National Institute of Public Health have shown more than a threefold increase in the use of medication for ADHD since 2004 (3). The condition has only a few options for evidence-based treatment, including pharmacotherapy, behavioural intervention, psychotherapy interventions and School-based interventions (2). Pharmacotherapy is currently considered as the cornerstone of evidence-based treatment for ADHD, and over 70% of affected children respond to psychostimulant medication (6). Nevertheless, there is a lack of evidence of long-term efficacy and the side effects associated with these pharmacological treatments have led to a search for other alternatives (7). Thus non-medical treatment is sought after by patients and parents alike.

Studies have shown an association between ADHD and Western dietary pattern (4), and there seems to be an increasing interest in whether diet influences on the symptoms or not. There are several approaches in ways of treating ADHD with diet, including change of the participants' entire diet, adding special groups of food to their diet, such as white fish, remove specific foods from the diet, such as sugar or food colourant, or adding one or several nutrients to the diet in form of capsules containing them. This review will focus on studies within this topic.

3 Methods

This study is written as an evaluation of published literature that has ADHD and diet as a topic. The collection of studies to be reviewed was selected by a search in PubMed, U.S National Library of Medicine National Institutes of Health, 2019-06-21, using the search strategy “Attention Deficit Disorder with Hyperactivity [mh] AND (Diet [mh] OR food [mh]).” Inclusion criteria were articles published after 2013-12-31 with full text available. The described research had to be done on humans between 0-18 years, and could not be based on prenatal status, mother’s health during pregnancy or way of birth. The search was further limited to clinical trials, reviews and meta-analyses. Trials were included if they examined treatment regiments for ADHD, and were randomized and placebo-controlled trials.

Among the resulting 62 articles, there were a few letters or comments to other published articles. These were not included nor reviewed. The search also resulted in articles with topics that included the search words but did not study diet as the treatment of ADHD, and were therefore not included. The final resulting number of articles was 20.

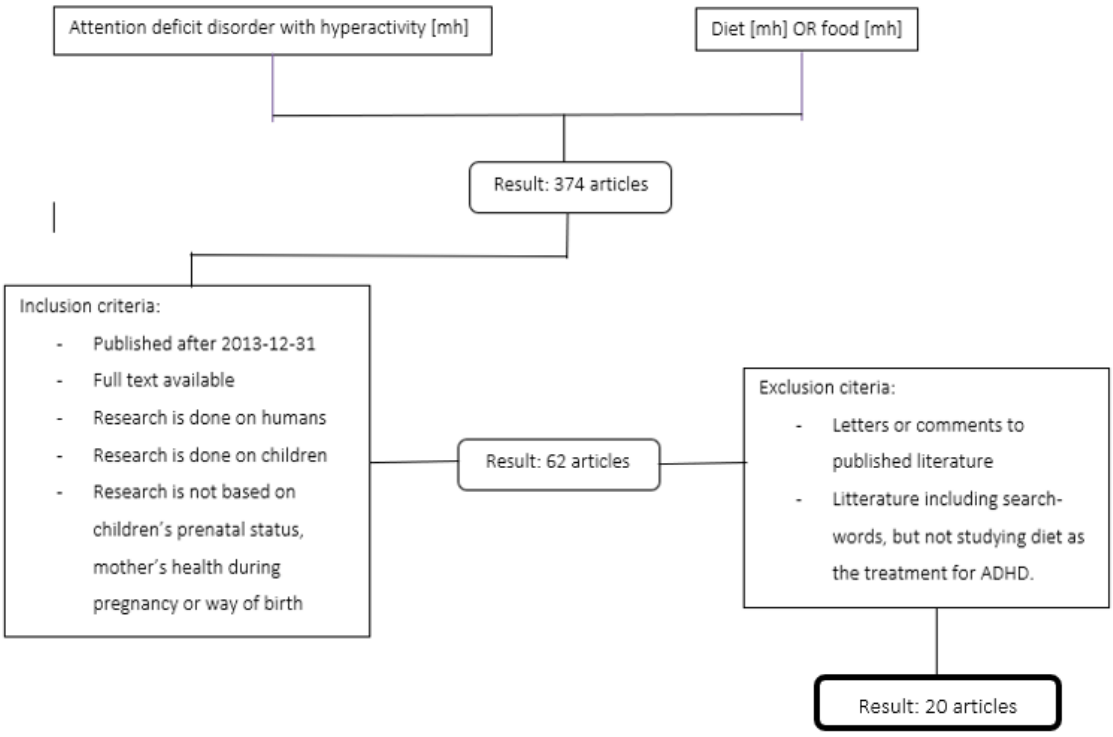

Fig 1: Flow of search in PubMed.

4 Results

The result consists of 20 articles studying different nutritional ways to treat ADHD. The outcome has been categorized according to which foods the authors propose as treatment.

Way of treatment	Number of articles
Polyunsaturated fatty acids	10
Micronutrients	3
Antioxidants	1
Probiotics	1
Algae	1
Whole diets	4

Fig. 2: Table of how the articles distribute between the proposed ways of treatment.

4.1 Dietary supplements

4.1.1 Polyunsaturated Fatty Acids

The majority of the articles reviewed, ten in total, involved the study of polyunsaturated fatty acids, PUFA, as the treatment for ADHD. PUFA's are essential acids, that cannot be synthesized by humans and thus are required in our diet (8). Eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA, are the two main bioactive forms of omega-3 polyunsaturated fatty acids in humans. These can be synthesized from the essential fatty acid α-linolenic acid. Omega-3 PUFAs are generally associated with anti-inflammatory effects, in comparison to omega-6 PUFAs, synthesized from the essential fatty acid linoleic acid, which are linked to pro-inflammatory effects (9). A high omega-6 to omega-3 fatty acid ratio could promote inflammation in the human body, including neuroinflammation. Increased omega-3 fatty acid concentration may alter central nervous system cell membrane fluidity and phospholipid composition, which may change the structure and function of the proteins embedded in it. The neurotransmission of dopamine and serotonin have shown to be affected by increased omega-3 fatty acids concentration in the cell and may be of importance in ADHD pathogenesis. Omega-3 fatty acids may also potentially reduce oxidative stress, which has been demonstrated to be elevated in ADHD (10).

The importance of omega-3 fatty acids in neural brain tissues is strongly suggested by membrane enrichment in these tissues. In the adult frontal cortex, the total amount of fatty acid consists of 15-20% DHA, and in neural tissues, it makes upward of 50% of polyunsaturates. These enrichments play an essential role in assuring the correct environment for membrane protein function and membrane fluidity. Deficiency of omega-3 fatty acids promotes a destructive effect related to brain and neurologic function, including inhibition of brain maturation and neuroplasticity and abnormalities in neurotransmitter function. If the deficiency occurs during neural development, it might give persistent adverse

developmental outcome. Fatty acid pools are directly influenced by dietary fatty acid intake. Dietary supplementations with fish oil results in an increased proportion of EPA and DHA within biological membranes, frequently at the expense of arachidonic acid. When dietary omega-3 levels are low, an imbalance of pro-inflammatory eicosanoids may occur as eicosanoids such as prostaglandins, thromboxane, and other oxidative metabolites derived from arachidonic acid, facilitate neuroinflammation. EPA and DHA are metabolized to resolvins and protectins, which are recently identified molecules, seen to be very potent anti-inflammatory mediators in cellular and animal model systems (11,12).

Widenhorn-Muller *et al*. (13) found that supplementation with mixes of omega-3 fatty acids increased EPA and DHA concentrations in erythrocyte membranes and this correlated significantly with improved memory function in 46 children diagnosed with ADHD according to DSM-IV criteria. The improved working memory also correlated significantly with decreased arachidonic acid, but supplementation did not affect other cognitive measures nor parent and teacher-rated behaviour. There were no healthy control group in the study, and therefore it is not known if the effect is only seen in children with ADHD, or if this will be the result for whoever takes the supplement used in the study.

A review from the same year, written by Rucklidge and Kaplan (7), suggest that there in 2014 was CEBM, Oxford Centre of Evidence-Based Medicine, level-1 evidence demonstrating the efficacy of omega 3 fatty acids for the treatment of ADHD. The recommendation is supplementation with a dose of 1-2 g daily, with a substantial content of EPA within the formulation.

A review by Gumpricht and Rockway (12) on neurodevelopmental disorders, NDD, ADHD, as well as autism and apraxia, states that the compelling evidence for increased oxidative stress, altered antioxidant defences and neuroinflammation in these children gives a rationale for adding omega -3 fatty acids to these children's diet. Extensive literature suggests increased oxidative stress occurs in children with NDD. As a corollary to these findings, other researchers found reduced antioxidant defences. There is also evidence for reduced plasma levels of vitamin E in children with NDD. Thus, the combination of elevated oxidative stress

and reduced vitamin E levels in children with NDD strongly suggests a need for both vitamin E and omega-3 fatty acids as a complementary nutritional therapeutic intervention in these children.

A randomized three-way crossover trial by Milte, Paletta and Buckley *et al*. (14), done in 87 children aged 6-13 years with ADHD symptoms, compared the effects of supplementation with long-chain n-3 PUFAs EPA and DHA with the omega-6 PUFA linoleic acid on literacy, attention and behaviour in children with ADHD with and without learning difficulties. A correlation was found with regression analysis of blood sample results between increased erythrocyte levels of omega-3 and omega-6 PUFA and outcome measures: There were negative associations between increased levels of omega-6 PUFA and various outcome variables, while increased levels of omega-3 PUFAs were associated with improved literacy, attention and parent-rated behaviour. A reduction in the ratio between omega-6 and omega-3 PUFA were therefore a consistent predictor of improved outcomes.

A meta-analysis published in 2015 by Cooper *et al*. (15) examined the efficacy of omega-3 PUFA supplementation on cognitive performance measures in school-aged children and adults who were typically developing or had ADHD, or related neurodevelopmental disorder. There was not found an effect of the supplementation on cognition in the whole group, or the groups analysed separately. A small improvement in short-term memory and working memory was seen, in a few studies, in participants with low omega-3 PUFA.

In a double-blind randomized controlled trial by Bos, Oranje, Veerhoek *et al*. (16) Omega-3 PUFA dietary supplementation improved symptoms of inattention in boys with and without ADHD. The dopamine turnover and neural activity did not change during the intervention; therefore the effect did not appear to be mediated by dopaminergic cognitive control networks. This indicates that typically developing children also benefit from the intervention, and therefore supplementation with omega-3 seems to be important for all children. The finding that the result is not mediated by dopaminergic cognitive control measures correlates with the findings of Bergwerff and Luman *et al*. (17) who found that children with ADHD showed normal values of aromatic amino acids in blood spots and urine, and had a normal

protein intake compared to controls. The aromatic amino acids tryptophan, tyrosine and phenylalanine are essential in the synthesis of serotonin and dopamine, but no association between the disorder's symptoms and the concentration of these substances were found.

A meta-analysis from 2016 by Cooper, Tye *et al*. (18) studied the effect of omega-3 PUFA supplementation on emotional liability, defined as low frustration tolerance, irritability and mood liability. Initial analyses gave no significant effects on emotional liability, oppositional behaviour, conduct problems and aggression. However significant effects were seen in subgroup analyses on parent-rated emotional liability in studies that met strict inclusion criteria. Tendencies of improvement on teacher-rated oppositional behaviour in studies supplemented with adequate EPA were also seen. Only a few studies (n=10) with enough data could be included in the analysis, which the authors point out as a demonstration of the need of further research in the area to gain a more conclusive picture.

In a randomised, double-blind, placebo-controlled trial by Kean, Sarris *et al*. (19) found that a marine oil extract rich in long-chain polyunsaturated fatty acids, named PCSO-524, did not improve parent-rated levels of hyperactivity, inattention and impulsivity over placebo in children with ADHD, but all children consuming the product significantly improved in cognitive tasks compared to the group consuming placebo.

A randomized, placebo-controlled clinical trial by Crippa, Tesei *et al*. (20) studying the efficacy of a 6-month supplementation with DHA as the only treatment in 50 medication-naïve school-children with ADHD. The primary outcome measure did not show benefit of the treatment on an ADHD parent rating scale. Secondary behavioural outcome showed statistically significant effects on psychosocial function and a decrease in parent-rated emotional problems, although the size of these effects, 0.13 and 0.23, were quite small. All the children in the trial had abnormally lower blood levels of DHA at baseline compared to 22 normal developing peers matched by IQ, age and gender. The authors state that the study is limited by its small sample size and significant between-groups differences at baseline.

4.1.2 Micronutrients

There are many metabolic steps in every pathway of neurotransmitters, where each step requires enzymes. These enzymes are dependent on multiple and adequate quantities of vitamins and minerals, cofactors. Inborn metabolic dysfunction which limits availability of micronutrient cofactors, resulting in slow metabolic activity, might cause the psychiatric symptoms seen in ADHD (21,22). ATP production is possibly compromised in ADHD, which could explain micronutrients potential therapeutic effects through improved mitochondrial production of adenosine triphosphate, ATP. Higher production of ATP would give improved energy metabolism of neurons and glial cells (7).

Trials of treatment with vitamins and minerals have mainly focused on single nutrients, often resulting in mixed and inconsistent effects, most often negligible. This suggests that single nutrient interventions do not have an adequate impact on the complex biochemical pathway in children with ADHD. An administration of one nutrient could cause an imbalance in other, and it is unlikely that a single nutrient would resolve such a complex disorder (7).

The most frequent micronutrients studied in children with ADHD are zinc and iron. Zinc is involved in the metabolism of melatonin, prostaglandins and neurotransmitters (23,24). Symptoms of zinc deficiency mimic the symptoms of ADHD, and most meta-analyses suggest an association between the two. Several clinical trials have shown that zinc supplements are superior to placebo in reducing hyperactivity and impulsivity (25). Zinc might also improve the effect of amphetamine, the most common ADHD drug (26). This suggests that zinc plays an important role in the pathogenesis of ADHD. Iron is a cofactor for the rate-limiting step of monoamine synthesis, and therefore critical to producing dopamine and norepinephrine. Several studies have shown a correlation between low serum iron levels and ADHD, iron deficiency increasing symptoms and iron supplements improving them (25). A case-control study by Yang, Zhang *et al*. (25), the level of zinc was observed significantly lower in ADHD group than that in the control group, and they found a moderate correlation between zinc level and inattention. None of the other elements, including iron, copper, magnesium and lead, showed a significant relation to ADHD.

As mentioned earlier, according to Gumpricht and Rockway (12), there is evidence for reduced plasma levels of vitamin E in children with neurodevelopmental disorders. The primary function of vitamin E is to protect membrane polyunsaturated fatty acids against oxidative damage and is particularly important in omega-3 fatty acid-enriched neurologic tissues. Symptoms of ADHD may frequently overlap with the neurologic symptoms observed in vitamin E-deficient patients, although obvious human vitamin E deficiency is only seen in individuals with either severe malnutrition or fat malabsorption syndromes, such as children with cystic fibrosis or cholestatic liver disease.

An open-label reversal design study by Gordon, Rucklidge, Blampied *et al*. (27) studied the effect of a micronutrient supplement containing 36 different vitamins and minerals; Vitamins A, B1-6 + 9 and 12, C, D, E and H, and calcium, iron, phosphorus, iodine, magnesium, zinc, selenium, copper, manganese, chromium, molybdenum and potassium. It also contained dl-phenylalanine, glutamine, citrus bioflavonoids, grape seed, choline bitartrate, inositol, ginkgo biloba, methionine, germanium sesquioxide, boron, nickel, and vanadium. During a 6-month trial, 14 children with the diagnosis of ADHD, were given this supplement for eight weeks, then had no treatment for four weeks, and then treatment for eight new weeks, before the treatment was withdrawn for the last four weeks. While taking micronutrients, the great majority of participants experienced a statistically and clinically significant reduction in ADHD symptoms, improvement in mood, and increase in overall functioning that were reversed when the treatment was withdrawn. Benefit was observed by the parents, clinicians, and the children themselves. Participants, caregivers and clinicians knew when they were taking and not taking the micronutrient, which means the positive responses given may have been influenced by expectancy of effect. The contribution of placebo response to the observed results cannot be estimated, but a convincing reason why a placebo effect is unlikely to explain the entire therapeutic results is that for most participants, the therapeutic effect was gradual, with the most benefit shown several weeks after starting the micronutrients.

4.1.3 Antioxidants

Different *in vivo* mechanisms generate reactive oxygen species, ROS, that oxidise agents or are easily converted into radicals (28). Mitochondrial energy production is the main source of ROS throughout the body, but other reactions contribute. In the central nervous system, activated microglia is also an important source (29). ROS are required in low levels for normal cell functioning, but radicals are highly reactive, and excess of ROS can therefore damage the macromolecules of the cell, and thereby their function (30). A way of reducing free radicals in the body is by detoxification by antioxidants (31). A shift in the balance between oxidants and antioxidants in favour of oxidants is called oxidative stress, which can damage for example macromolecules and DNA (32). ADHD aetiology can be related to multiple effects of oxidative stress on the brain, as it can lead to progressive neuronal damage and weakening of normal cerebral functions (33).

A review by Verlaet, Maasakkers *et al*. (30) concludes that a nutritional supplement of antioxidants is a potential ADHD therapy as there is a proven association between ADHD and oxidant-antioxidant imbalances.

4.1.4 Probiotics

It is well recognized that gut microbiota affects the brain's physiological, behavioural and cognitive functions, although the exact mechanism of the gut microbiota-brain axis has not yet been fully understood. Evidence from animals and human studies has shown that microbiota of the gut has an important role in developing behaviour and cognitive functions by producing hormones, immune factors and metabolites, which also indicates that altering gut microbiota may improve or cure brain disease (34).

A prospective cohort study by Pärtty *et al*. (35) found that administration of *Lactobacillus rhamnosus GG* may reduce the risk of ADHD and Asperger's syndrome. A group of 132 infants were randomized to receive the bacteria or placebo during the first 6 months of life and were followed up for 13 years. The groups were equal at baseline, and although 57 were lost to follow-up, the groups were also equal at the end of the trial, except for duration of exclusive breastfeeding. At the age of 13 years, ADHD was diagnosed in 6 out of 35 children in the placebo group and none in the probiotic group. The mean numbers of *Bifidobacterium*

species bacteria, which in mice have shown to have an anxiolytic effect, was significantly lower in the faeces of the affected children in the first 6 months of life.

4.1.5 Other

Cremonte, Sisti *et al*. (36) did an experimental study on supplementation with the algae extract Klamin in children with ADHD. The underlying theory was that current research suggests that ADHD can be attributed to interaction between dysfunctional neurotransmitter systems, and low levels of phenylethylamine, PEA, which is an endogenous neurotransmitter that is normally stored and metabolized in the brain. Klamin contains PEA, which stimulates the release of dopamine and catecholamines from intraneuronal reserves in the brain, and inhibition of the reuptake of noradrenaline, serotonin and dopamine in neurons. PEA is easily degraded by monoamine oxidase B, MAO B, but Klamin also contains AFA-phycocyanins, which is a selective inhibitor of this enzyme. Despite the small study it appears to confirm the initial hypothesis that Klamin may positively affect the expressions of ADHD symptoms.

4.2 Dietary patterns

A few studies in the search did not study a nutrient or supplement, but a whole diet and its association to ADHD. A case-control study by Zhou, Wu *et al*. (37) on Chinese children found some interesting associations between ADHD and diets: Dietary patterns rich in deep water fish, shellfish, freshwater fish, fungi and algae, white meat, and organ meat was inversely associated with ADHD. The same association was found in dietary patterns rich in zinc, phosphorus, riboflavin, selenium, calcium and protein. Additionally, ADHD was negatively related to blood levels of zinc. The study suggests, and support its suggestion with previous studies, that healthy dietary patterns, containing vegetable, fresh fruit, fish, white meat and whole grains were protective against ADHD, whilst an unhealthy dietary pattern, including fast food, ice cream, sweets, snacks and red meat were adversely related to ADHD. Another Case-control study by Ríos-Hernández, Alda *et al*. (38) and a cross-sectional study by Martín, Olivares *et al*. (39) found that lower adherence to the Mediterranean diet was associated with ADHD diagnosis, and raise the question whether a Mediterranean diet can prevent ADHD development.

A systematic review from 2015 by Rytter, Andersen *et al*. (40) looked into elimination diet, specifically diets without artificial colours and other additives. The studies reviewed did not provide any clear or convincing results concerning children with ADHD, however, two large studies both found that normal children showed an increase in ADHD-like behaviour after receiving a mix of artificial colourants, called “azo-dyes”, together with preservative sodium benzoate. The result of this is that the European Union have a law stating that foods containing these dyes should have a label warning that they may affect children’s behaviour and attention. Meta-analyses reviewed on this issue all concluded that food colourants have a small, but statistically significant, effect on ADHD symptoms in some children, although the studies were of limited quality. The review also contained five crossover RCT concerning short term exposure to sugar and artificial sweeteners, which found no change in core ADHD symptoms with either of them.

5 Discussion

The result of this study does not give a definite answer around diet as the treatment for ADHD, nevertheless, it points out some interesting findings for further investigation:

Several of the studies reviewed about polyunsaturated fatty acids found increased memory function when taking omega-3 supplements, but the studies do not determine whether this is an effect in children with ADHD only, or all developing children (13,15). Compelling evidence of oxidative stress, reduced antioxidant defences and neuroinflammation in children with ADHD gives rationale for adding PUFAs to these children’s diet, and in 2014 cumulative evidence suggested supplementation with 1-2g daily of omega-3 fatty acids with a substantial amount of EPA (7,12). Adequate EPA in the supplement also showed a trend of reduced emotional liability and teacher-rated oppositional behaviour (18). Supplementation with n-3 PUFAs compared with n-6 PUFAs improved literacy, attention and behaviour, and a reduced omega-6:omega-3 ratio was a predictor for an improved outcome (14).

Regarding micronutrients, trials with single nutrients often resulted in mixed and inconsistent findings. Supplementation with one nutrient could give imbalance in another, and therefore it

is unlikely that a single nutrient would resolve such a complex disorder (7). Clinical trials showed zinc to be superior of placebo in reducing hyperactivity and impulsivity, and it might improve the effect of amphetamine as treatment for ADHD. The study also found significantly lower levels of zinc in children with ADHD then controls, and there was a moderate correlation between blood zinc level and inattention (25,26,37).

There is evidence for reduced vitamin E in children with neurodevelopmental disorders, and symptoms of ADHD overlap with symptoms of Vitamin E deficiency (12).

A micronutrient containing 36 different vitamins and minerals gave the majority of participants, who were not blinded, a gradual therapeutic effect of reduced symptoms, mood and overall functioning reported by caretakers, teachers and the children themselves. Arguments for that the observed effect is not all placebo, are the gradual effect seen when taking the supplement (27).

Two case-control studies studying whole diets found inverse associations between ADHD and diets containing vegetable, fresh fruit, fish, white meat and whole grains, whilst an unhealthy dietary pattern, including fast food, ice cream, sweets, snacks and red meat were adversely related to ADHD. Inverse association were also found in dietary patterns rich in zinc, phosphorus, riboflavin, selenium, calcium and protein (37,38).

The use of PubMed as a search engine was chosen because it is standard for medical literature.

A strength of this study is that it is a systematic review of the subject. The study could also be done as an interview or a survey of treatment personnel. The benefit of using peer-reviewed articles is that it will give a general view of current evidence. Reviews of current evidence are important in the path forward in clinical research. An interview or survey, on the other hand, might have given a picture of the current experiences among therapist on the effect of diet as the treatment for ADHD, but the result would be from a local, at best national, point of view, and not be transmissible to the general population.

Another strength is that it pertains to existing results from child studies and not extrapolating on results from adult studies. Research on children for sake of finding treatment for children is also a key in clinical research. Though one can imagine a certain hesitance on performing research on children, the clinical research in field paediatrics needs to acknowledge the necessity for more clinical paediatric research.

A limitation of this study is that the search gave a low number of articles and that several of the included studies have small sample sizes. The only supplement with a tolerably number of studies where found on polyunsaturated fatty acids, where there were found nine, but other supplements or diets only had up to three articles. The primary reason for this is that the inclusion criteria might be too limitable. The first criteria were that the article was published in 2014 or later. By excepting articles published further back in time there would be more data to review. Second, the search was limited to humans, specifically children. The reason for this is that it might be difficult to know if results are transferable to humans if done on animals. The same goes for excluding studies done on adults, although it would be interesting to compare findings in adults versus children and see if the trends found in this study also are present in adults. The reason for excluding research done on prenatal health, mothers health during pregnancy and way of birth is that it cannot be used as treatment.

6 Conclusion

Although there is compelling evidence for omega-3 as a treatment for ADHD, the effects of other nutritional supplements as well as whole diets is not negligible and suggest not only specific nutrients but also whole diets should be considered both preventive and as the treatment for ADHD.

Some of the challenges in clinical research is that nutritional interventions, including dietary eliminations, demand resources, compliance and long-time follow-ups. Studies with greater sample sizes and more controlled trials are needed to show effects that can be sufficient to cause changes in clinical recommendations.

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8 Appendix: GRADE

<table>
<tr><td colspan="3">Reference: Widenhorn-Muller, K., Schwanda, S., Scholz, E., Spitzer, M., & Bode, H. (2014). Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins, Leukotrienes, and Essential Fatty Acids, 91(1–2), 49–60. https://doi.org/10.1016/j.plefa.2014.04.004</td><td>Study design: RCT
Grade - quality Moderate - IIa</td></tr>
<tr><td>Objective</td><td>Materials and methods</td><td>Results</td><td>Discussion/comments/Checklist</td></tr>
<tr><td>To determine whether supplementation with the long-chain omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acid affects behavioural symptomes and cognitive impairments in children 6-12 years of age diagnosed with attention-deficit/ hyperactivity disorder.
Conclusion
The positive effect of EPA/DHA supplementation on working memory function might not be specific for children diagnosed with ADHD. Definite conclusion about the effect can therefore not be drawn.
Country
Germany
Year collecting data
2013</td><td>Study design: Randomized, double-blind placebo-controlled trial involving parallel treatment for 16 weeks.
Participants: Children of both sexes 6-12 years of age, meeting the criteria of ADHD. Recruited by informing the parents of children with diagnosed, or suspected, ADHD through health professionals about the possibility to participate in the study.
Procedure:
1. Parent-rated and teacher-rated questionnaires comprised of 20 items corresponding to the ICD-10 and DSM-IV criteria for ADHD.
2. Anamnestic interview with the children and the caretakers, to address behavioural symptoms, and social and medical background.
3. General cognitive ability and attentional performance, together with behaviour during study visits, were assessed by psychologist.
4. Only children fulfilling the DSM-IV criteria were invited for the next face of the study.
5. Pre-interventional blood test.
6. Medical examination to exclude the possibility that the behavioural impairment was caused by other conditions.
7. Questionnaire addressing fish and sea food consumption last four weeks.
8. 16 weeks intervention with capsules and intake protocols.
9. Post interventional questionnaire addressing fish and sea food consumption last four weeks.
10. Post interventional behavioural rating by teachers and parent, and behavioural and cognitive assessment by the same professional who had done pre-interventional testing.
11. Post-interventional blood test.</td><td>Supplementation with the omega-3 fatty acid mixes increased EPA and DHA concentrations in erythrocyte membranes and improved working memory function but had no effect on other cognitive measures and parent- and teacher-rated behaviour in the study population. Improved working memory correlated significantly with increased EPA, DHA and decreased arachidonic acid (AA).</td><td>Is the objective of the study explicit? Yes.

Who is included/excluded? Included: Children 6-12 years of age meeting DSM-IV criteria of ADHD. Excluded: IQ ≤ 70, use of stimulant medication or other psychoactive medications as well as fatty acid supplementation used within the previous 6 months. Children with allergies against fish or fish products.

Randomization? Computer-generated random sequence to allocate participants to either supplement or placebo group.

Where all participants given an account for at the end of the trial? Yes.
Where participants/Study personnel blinded to intervention condition? Yes
Where the groups equal at the start? Yes
Where the groups treated equally? Yes

What are the results? Increased EPA/DHA, and reduced AA, improved working memory, but had no effect on other cognitive measures and parent- and teacher-rated behaviour in the study population.

Is the result clinically significant? No
Where all outcome measures assessed? Yes
Are the advantages worth the costs/disadvantages? Not relevant.

What do the authors discuss as strengths/weaknesses? Strengths: 59% where informed by psychiatrist, which requires referral from a podiatrist, and therefor makes it unlikely that symptom severity was low. Intake protocols and fatty acid profiles where measures for adherence for study protocol, confirming high complience in both groups. Low attrition rate, 12%, compared to other studies. Weaknesses: Five of the children had problems swallowing the capsules, and five families had objections against pork gelatine capsule cast. A liquid form would be suitable for more children. Study is limited by small sample size. Participant selection through DSM-criteria limits comparison to studies using symptom severity. The positive effect on working memory found might not be specific for children diagnosed with ADHD.

Do the authors refer to other literature that strengthens or undermine the results? Yes
Do the results have plausible biologic explanations? Yes.</td></tr>
</table>

Reference: Milte CM, Parletta N, Buckley JD, Coates AM, Young RM, Howe PRC. Increased Erythrocyte Eicosapentaenoic Acid and Docosahexaenoic Acid Are Associated With Improved Attention and Behavior in Children With ADHD in a Randomized Controlled Three-Way Crossover Trial. J Atten Disord. 2015 Nov;19(11):954–64.			Study design: RCT	
			Grade - quality	High - IIa
Objective	**Materials and methods**	**Results**	**Discussion/comments/Checklist**	
To investigate effects of omega-3 polyunsaturated fatty acids, n-3 PUFA, docosahexaenoic acid, DHA, and eicosapentaenoic acid, EPA, on attention, literacy, and behaviour in children with ADHD. **Conclusion** Increasing erythrocyte DHA and EPA via dietary supplementation may improve behaviour, attention, and literacy in children with ADHD. **Country** Australia **Year collecting data** 2007-2009	A 12-month randomized trial controlled three-way crossover trial in children aged 6-13 years with ADHD symptoms. Children were recruited through media releases and television interviews, newspaper advertisements, school newsletters, and flyers. By brief screening interview over the phone, 115 children were deemed eligible and their parents and guardians were sent information sheets and consent forms. Parents of children without diagnosis of ADHD were asked to complete an ADHD index. Children were independently allocated to one of three treatment conditions using the process of randomization by minimization on the basis of age and gender. Each condition received the two omega-3 rich oils, EPA-rich and DHA-rich, and control oil, LA-rich, for 4 months each. The three treatment conditions comprised EPA-DHA-LA, DHA-LA-EPA, or LA-EPA-DHA. Study investigators, parents, and children were blinded to the randomization until completion of data collection analysis. Assessment of the children were done at baseline, 4, 8, and 12 months. Capsule containers were returned at each visit for complience assessment by capsule counting. At each visit fasted blood samples were collected, and the children underwent a 30 to 45 min cognitive assessment. Between each visit, parents were contacted via phone or email at least 3 times by researchers to reduce dropouts, informally check compliance and report any adverse events.	Fifty-three children completed the treatment. Outcome measures showed no significant differences between the three treatments. However, in children with blood samples (n = 76-46), increased erythrocyte EPA + DHA was associated with improved spelling (r = .365, p < .001) and attention (r = −.540, p < .001) and reduced oppositional behaviour (r = −.301, p < .003), hyperactivity (r = −.310, p < .001), cognitive problems (r = −.326, p < .001), *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*) hyperactivity (r = −.270, p = .002) and *DSM-IV* inattention (r = −.343, p < .001).	**Is the objective of the study explicit?** Yes **Who is included/excluded?** Included: Children with diagnosis of ADHD or parent-rated symptoms > 90th percentile on the Conners' Parent Rating Scale and parent-reported learning difficulties. Excluded: Children who had consumed n-3 PUFA supplements during the 3 months prior to the study or were tanking any ADHD medication. **Randomization?** Randomization by minimization on the basis of age and gender. **Where all participants given an account for at the end of the trial?** Yes. **Where participants/Study personnel blinded to intervention condition?** Yes. **Where the groups equal at the start?** Yes. **Where the groups treated equally?** The three groups received the three supplements at different times throughout the year but were other than that treated equal. **What are the results?** Increased levels of n-3 PUFAs (most consistently EPA + DHA together) were associated with improved literacy, attention, and parent-rated behaviour, while there were negative associations between increased n-6 PUFA levels and various outcome variables. Accordingly, reduction in the ratio of n-6:n-3 was a consistent predictor of improved outcomes. **Is the result clinically significant?** Yes. **Where all outcome measures assessed?** Yes. **Are the advantages worth the costs/disadvantages?** Yes. **What do the authors discuss as strengths/weaknesses?** Weaknesses: Considerable variability in supplement compliance. Small sample size. A possibility of no washout effect that were anticipated following each treatment, in particular DHA, did not go back to baseline after being ceased. If children experienced improvements in learning or behaviour following optimization of n-3 levels, a degree of that learning may be retained after cessation of supplementation. The order of the three treatments could have interacted with any carryover effects given that only three out of six possible orders were used. Strengths: Blood samples enabled to use a regression design to assess relationships between blood PUFA levels and outcome measures at each time point. Blood samples can confirm and account for degree of compliance and variability in baseline nutrient levels. **Do the authors refer to other literature that strengthens or undermine the results?** Yes. **Do the results have plausible biologic explanations?** Yes.	

Reference: Gordon HA, Rucklidge JJ, Blampied NM, Johnstone JM. Clinically Significant Symptom Reduction in Children with Attention-Deficit/Hyperactivity Disorder Treated with Micronutrients: An Open-Label Reversal Design Study. J Child Adolesc Psychopharmacol. 2015 Dec;25(10):783–98.			Study design: RCT – open-label reversal design.
			Grade – quality	Moderate - IIIa
Objective	**Materials and methods**	**Results**	**Discussion/comments/Checklist**
The purpose of this study was to investigate the clinical effect and safety of a broad spectrum, 36 ingredient micronutrient (vitamins and minerals) in treating children with attention-deficit/hyperactivity disorder (ADHD). **Conclusion** This study demonstrates the clinical benefit, feasibility, and safety of broad-spectrum micronutrients in the treatment of childhood ADHD. Replications utilizing double-blind placebo-controlled studies are warranted. **Country** New Zealand **Year collecting data** September 2011 to January 2013.	This open-label, on-off-on-off (reversal design) study followed 14 participants (8–12 years of age) with ADHD, diagnosed using standardized instruments, for 6 months with no dropouts. Following baseline assessment, including haematology and biochemistry screening, participants began an 8-week treatment phase with micronutrients titrated up to maximum dose (15 capsules/day). Treatment was withdrawn for 4 weeks, reinstated for a further 8 weeks, and then withdrawn for 4 weeks. Primary outcomes included the Conners' Parent Rating Scale, the Clinical Global Impressions Scale (CGI), and the Strengths and Difficulties Questionnaire – Parent version (SDQ). Secondary outcomes were mood and global functioning.	Modified Brinley plots revealed a reduction in ADHD symptoms, improved mood, and improved overall functioning during intervention phases, and deterioration in ADHD symptoms, mood, and overall functioning during the withdrawal phases. Reliable change analyses, Cohen's d and percent superiority effect sizes, 95% confidence intervals and t tests confirmed clinically and statistically significant change between the intervention and withdrawal phases, with large effect sizes observed pre- to post-exposure of micronutrients (d = 1.2–2.2) on ADHD symptoms during intervention phases. Seventy-one percent of participants showed at least a 30% decrease in ADHD symptoms by the end of the second treatment phase, and 79% were identified as "much improved" or "very much improved" at the end of the second phase (5 months) based on the clinician-rated CGI when considering functioning generally. The SDQ showed that these benefits occurred across other areas of functioning including emotional symptoms, conduct problems, and prosocial behaviours. The children's self-reports confirmed the improvements. Excellent adherence to treatment occurred throughout, side effects were mild and transitory, and no safety issues were identified through blood analyses.	**Is the objective of the study explicit?** Yes. **Who is included/excluded? Included:** Participants who met the criteria for ADHD based on the Diagnostic and Statistical Manual of Mental Disorders 4th ed., Text Revision (DSM-IV-TR) and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime version, a semi structured interview conducted with participants and their parents/caregivers. Participants were also required to have an elevated level on one or more of the ADHD subscales of the Parent or Teacher Conners Rating Scale. **Excluded:** Participants who initially had abnormal blood work and was unwilling to repeat, who were unable to complete blood test prior to trial start, who decided to buy the product independently of the trial and those who currently were taking psychiatric medication. **Randomization?** No, all participants got the same treatment. **Where all participants given an account for at the end of the trial?** Yes. **Where participants/Study personnel blinded to intervention condition?** No, this was an open label trial. **Where the groups equal at the start?** Not relevant. **Where the groups treated equally?** Not relevant. **What are the results?** While taking micronutrients, the great majority of participants experienced clinically significant reductions in ADHD symptoms, improvements in mood, and increases in overall functioning that were reversed when the treatment was withdrawn. Benefit was observed across all three sources of information: parents, clinicians, and the children themselves. **Is the result clinically significant?** Yes. **Where all outcome measures assessed?** Yes. **Are the advantages worth the costs/disadvantages?** Yes. **What do the authors discuss as strengths/weaknesses? Strengths:** Research design is recognized as appropriate for establishing treatment efficacy, excellent adherence and no study dropouts. Sample was reflective of children typically seen in clinical practice with high rate of co-occurring diagnoses and previous unsuccessful treatment with medications, participants came from diverse socioeconomic status. This enhance the potential of generalization of the results. **Weaknesses**: A large amount of data was missing because of phase changes falling during holidays, and other timing factors. Participants, caregivers and clinicians knew when they were taking and not taking the micronutrient, which means the positive responses given may have been influenced by expectancy of effect. The contribution of a placebo response to the observed results cannot be estimated, but a convincing reason why a placebo effect is unlikely to explain the entire therapeutic results is that for most participants, the therapeutic effect was gradual, with the most benefit shown several weeks after starting the micronutrients. **Do the authors refer to other literature that strengthens or undermine the results?** Yes. **Do the results have plausible biologic explanations?** Yes.

Reference: Partty A, Kalliomaki M, Wacklin P, Salminen S, Isolauri E. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatr Res. 2015 Jun;77(6):823–8.			Study design: Cohort.	
			Grade - quality	Moderate - IVa
Objective	**Materials and methods**	**Results**	**Discussion/comments/Checklist**	
To test the hypothetical involvement of the gut brain-axis in the manifestation of ADHD and Asperger's syndrome. **Conclusion** Probiotic supplementation early in life may reduce the risk of neuropsychiatric disorder development later in childhood possible by mechanisms not limited to gut microbiotacomposition. **Country** Finland **Year collecting data** February 1997 to October 2011	Seventy-five infants who were randomized to receive *Lactobacillus rhamnosus* GG or placebo during the first 6 months of life were followed-up for 13 years. Gut microbiota was assessed at the age of 3 weeks, 3, 6, 12, 18, 24 months, and 13 years using fluorescein in situ hybridization (FISH) and qPCR, and indirectly by determining the blood group secretor type at the age of 13 years. The diagnoses of attention deficit hyperactivity disorder (ADHD) and Asperger syndrome (AS) by a child neurologist or psychiatrist was based on ICD-10 diagnostic criteria.	ADHD or Asperger syndrome was diagnosed in 6 out of 35 children in the placebo group by the age of 13 years, and none in the probiotic group. All children with a diagnosis were male, but result remained significant (P=0.02) when corrected for gender. The number of *Bifidobacterium longum*, assessed by qPCR, at the age of 3 months was lower in the children with neuropsychiatric disorders than in healthy children (4.35 (3.99–10.40) log/g and 10.18 (8.88–10.88) log/g, respectively, P = 0.045). At 6 months, after completing probiotic intervention the mean number of cells belonging to the genus Bifidobacterium as measured with FISH was significantly lower among children with neuropsychiatric disorders than in those without (8.26 (1.24) log cells/g vs. 9.12 (0.64) log cells/g, respectively, P = 0.03). At the age of 18 months, the mean numbers of Bacteroides and Lactobacillus-Enterococcus group bacteria were lower among children with ADHD/AS than healthy children (7.28 (0.85) log cells/g vs. 8.13 (0.51) log cells/g, P = 0.008; 7.71 (0.78) log cells/g vs. 8.40 (0.40) log cells/g, P = 0.01, respectively. Furthermore, at the age of 24 months, the mean numbers of cells belonging to the Clostridium histolyticum group were lower among children with ADHD or AS than in healthy children, (7.46 (0.44) log cells/g vs. 8.16 (0.55) log cells/g; P = 0.04). At the age of 13, there were no statistically significant differences in gut microbiota composition, analysed with FISH or qPCR, between children with or without neuropsychiatric disorders.	**Is the objective of the study explicit?** Yes **Where the groups of the study recruited from the same population?** Yes. **Where the subgroups selected equivalent to the population at large in terms of their key characteristics?** Yes. **Where the participants representative for a defined population?** Yes. **Where outcome measures assessed similarly in the two subgroups?** Yes. **Where the person assessing the result blinded to the group identification?** Yes. **Where the study prospective?** Yes. **Where there an equal distribution of participants lost to follow-up between the two groups?** No. **Where eventual attrition bias evaluated?** Yes. **Where the follow-up time long enough to establish positive or negative outcomes?** Yes. **Is confounding factors in design, carry out and analysis taken into consideration?** Yes. **What are the results?** At the age of 13 years, ADHD or AS was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group ($P = 0.008$). The mean (SD) numbers of *Bifidobacterium* species bacteria in feces during the first 6 mo of life was lower in affected children 8.26 (1.24) log cells/g than in healthy children 9.12 (0.64) log cells/g; $P = 0.03$. **Do you believe the results are true?** Yes. **What do the authors discuss as strengths/weaknesses? Strengths:** A long follow-up. The gut microbiota has been analysed comprehensively by FISH and qPCR as well as indirectly by blood group secretor type analysis. **Weaknesses:** The number of dropouts were considerable during the follow-up. Therefore, the authors cannot discount the possibility that the issue not have biased the findings. However, the number of dropouts was equally divided in the intervention groups and base-line characteristics of the dropouts and the study finisher were similar, except for duration of exclusive breast-feeding, demonstrating that these groups were unbiased in almost all of the known factors. **Do the authors refer to other literature that strengthens or undermine the results?** Yes. **Is the result clinically significant?** No.	

<table>
<tr><td colspan="3">Reference: Bos DJ, Oranje B, Veerhoek ES, Van Diepen RM, Weusten JM, Demmelmair H, et al. Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology. 2015 Sep;40(10):2298–306.</td><td>Study design: RCT</td></tr>
<tr><td colspan="3"></td><td>Grade – quality</td><td>Moderate - IIIa</td></tr>
<tr><td>Objective</td><td>Materials and methods</td><td>Results</td><td colspan="2">Discussion/comments/Checklist</td></tr>
<tr><td>To investigate the effects of dietary supplementation on ADHD symptomes and cognitive control in young boys with and without ADHD.

Conclusion

Dietary supplementation with omega-3 fatty acids reduces symptomes of ADHD, both for individuals with ADHD and typically developing children.

Country

The Netherlands

Year collecting data

Not known</td><td>40 boys with ADHD and 39 typically developing boys were recruited. Children on methylphenidate was instructed to not take medication 24 hours before an MRI scan, but they were allowed to use their medication throughout the intervention period. Intervention was a 16-week double-blind randomized placebo-controlled trial, where half of the group with ADHD received placebo, and the other half received omega-3 fortified margarine, and same for the reference group. Participants were instructed to consume 10g of margarine each day and complience was assessed by weighing the leftover product.
Cheek cell samples were collected to analyse phospholipid fatty acid levels. Urine samples were collected to measure the homovanillic acid to creatine ratio, as proxy for dopamine turnover. Severity and symptomes of ADHD was measured by checklists and rating scales. MRI were used to asses if the supplementation would increase activation in prefrontal and striatal areas.</td><td>Behavioral: Subjects with ADHD scored higher on scales for attention problems, rule breaking behaviour and aggressive behaviour then reference group. Scores on attention problems were reduced in the group who received supplementation, compared to the group who received placebo (p = 0.011). Group of typically developing did not show significant reduction in attention problems when receiving active treatment. There was no significant effect on rule breaking behaviour or aggressive behaviour.
MRI: No effect of dietary omega-3 supplementation on task performance or brain activation during the cognitive control task.</td><td colspan="2">Is the objective of the study explicit? Yes.

Who is included/excluded? Included: 40 boys between 8 and 14 years of age with a DSM-IV diagnosis of ADHD Only boys, to minimize potential cofounds. The children with ADHD was either medication naïve or using only methylphenidate. 39 typically developing boys matched to the patients age, parental education in years, hand preference and body mass index as a reference group. Excluded: Children with ADHD on other psychoactive medication.

Randomization? Double-blind randomized placebo-controlled design. Children with ADHD were randomized into two groups, and this were also done in the control group.

Where all participants given an account for at the end of the trial? Yes.
Where participants/Study personnel blinded to intervention condition? Yes.
Where the groups equal at the start? Yes.
Where the groups treated equally? Yes

What are the results? The study shows that dietary supplementation with omega-3 fatty acids reduces symptomes of ADHD, both for individuals with ADHD and typically developing children. This effect did not appear to be mediated by dopaminergic cognitive control networks, as measures of dopamine turnover and naural activity during cognitive control were unaffected by the intervention. The study offers support that omega-3 supplementation may be an effective augmentation for pharmacological treatments of ADHD.

Is the result clinically significant? Yes.
Where all outcome measures assessed? Yes.
Are the advantages worth the costs/disadvantages? Yes.

What do the authors discuss as strengths/weaknesses?
Strengths: Randomized placebo-controlled double-blind design. The inclusion of a typically developing reference group to assess whether effects were specific to ADHD.
Weaknesses: In some subjects the quality of the cheek cell samples did not permit a reliable detection of DHA. A small number of participants with ADHD had changes made to their medication during the intervention, although analysis showed that the intervention till held without these subjects. Sample sizes of MRI study were smaller then in the main study as a result of subject motion.

Do the authors refer to other literature that strengthens or undermine the results? Yes.
Do the results have plausible biologic explanations? Yes.</td></tr>
</table>

Reference: Zhou F, Wu F, Zou S, Chen Y, Feng C, Fan G. Dietary, Nutrient Patterns and Blood Essential Elements in Chinese Children with ADHD. Nutrients. 2016 Jun;8(6).			Study design: Case-control	
			Grade – quality:	Moderate - IVa
Objective	**Materials and methods**	**Results**	**Discussion/comments/Checklist**	
To investigate the association of dietary and nutrient patterns with the risk of ADHD. **Conclusion** The fish-white meat dietary pattern and mineral-protein dietary pattern may have beneficial effects on ADHD in Chinese children, and blood zinc may be helpful in distinguishing ADHD in Chinese children. **Country** China **Year collecting data** Not known	Participants were recruited from the Jiangxi Provincial Children's Hospital, from children attending paediatric clinics for health care and ADHD assessment. All the children were of Chinese Han nationality, aged 6-14 years at the time of the investigation and fulfilled the DSM-IV-R criteria of ADHD. Participants were excluded if there were any evidence of prenatal insults, autism, Asperger syndrome, epilepsy, schizophrenia, affective disorder pervasive developmental disorder, and mental retardation. The control children were randomly selectred from children receiving routine health care at the same clinics.	The authors identified four major dietary patterns and four major nutrient patterns for Chinese children. A fish-white meat dietary pattern rich in shellfish, deep water fish, white meat, freshwater fish, fungi and algae and organ meat was inversely associated with ADHD. Further analysis found that a mineral-protein nutrient pattern rich in zinc, protein, phosphorus, selenium, calcium and riboflavin was inversely associated with ADHD. Additionally, the blood zinc was also negatively related to ADHD.	**Is the objective of the study explicit?** Yes. **Is the case-control design suitable for the objective?** Yes **Are the cases recruited in a expedient way to elude selection bias?** Yes **Is the diagnosis validated?** Yes **Are the controls recruited in an expedient way?** Yes **Can it be ruled out that the control group have the disease in question?** Yes **Where the groups selected from similar populations?** Yes **Where there any differences between the two groups non-responders?** No **Where the two groups comparable on important confounding factors?** Yes and no **Is the primary exposure validated?** Yes **Where the groups treated equally?** Yes **Have the authors taken consideration to confounding factors in the design/analysis? Is the exposure for danger, harm and action measured and graded in a similar way in both groups?** Yes **Where the person collecting data blinded to who were case and who were control?** Yes **Do you believe in the results?** Yes **Can the results be transferred to practice?** Yes **Does the literature support the results?** Yes **What do the authors discuss as strengths/weaknesses? Weaknesses:** Several lifestyle factors and other risk factors for ADHD were significantly different between the case-groups and the control-groups. It was adjusted for using statistical analysis, but residual confounding was still unavoidable because of measurement errors and missing adjustments for several unmeasured factors. Food frequency questionnaire are known to contain a certain degree of measurement error. The four major dietary patterns derived from the data of the study only explained 32,5% of the total variance, suggesting the existence of other dietary patterns. Hospital-based controls are prone to selection bias. **Do the results have plausible biologic explanations?** Yes	