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Food intolerance and the few-foods (or oligoantigenic) diet in children with attention-deficit hyperactivity disorder

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ABSTRACT

The hypothesis that some children with attention-deficit hyperactivity disorder (ADHD) may show sensitivity or allergic reactions to various food items has led to the development of the the few-foods (or oligoantigenic) diet. The rationale of the diet is to eliminate certain foods from the diet in order to exclude potential allergens contained either naturally in food or in artificial ingredients with allergenic properties. The oligoantigenic diet attempts to identify individual foods to which a person might be sensitive. First, ADHD symptoms are monitored while multiple foods are excluded from the diet. Subsequently, if symptoms remit, foods are re-introduced, while observing the individual for the return of symptoms. An advantage of the oligoantigenic diet is that it can be tailored to the individual. A growing body of evidence suggests that behavioral symptoms of subgroups of children with ADHD may benefit from the elimination of certain foods. The effect sizes of an oligoantigenic diet regarding improvement of ADHD symptoms have been found to be medium to large. Available evidence suggests that the investigation of the role of food hypersensitivities in ADHD is a promising avenue worthy of further exploration. Further large-scale, randomized controlled studies including assessment of long-term outcome are therefore warranted.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric diagnoses in children and adolescents and is also increasingly diagnosed in adults[1]. In the general population, the prevalence of ADHD in children has been estimated to be 3.4%[1]. ADHD is complex, heterogeneous and multifactorial and is associated with widely diverse profiles of behavior, cognition, emotion and motivation. The main symptoms of ADHD include age-inappropriate levels of inattention, impulsivity and hyperactivity[1]. Comorbidity of ADHD with other mental conditions is frequently observed[2]. Genetic susceptibility interacting with social and environmental factors is assumed to contribute to the etiology of ADHD. Structural or functional brain changes cannot be found consistently in people diagnosed with ADHD, and both biological markers underpinning the validity of the ADHD concept and laboratory tests for psychiatric diagnosis are lacking[3-4]. Hence, the biological basis of ADHD is still poorly understood despite the very large number of genetic, neurochemical, neuroimaging and neurophysiological studies.

While psychostimulant medication, behavior therapy and parent management training may induce short-term improvements of inattention, hyperactivity and impulsivity in children and adolescents with ADHD, the degree of efficacy of these therapies remains a matter of debate[5]. Numerous trials have shown that pharmacotherapy administered for several weeks can produce statistically significant improvements of the main ADHD symptoms, as assessed using clinical rating scales, compared to placebo. However, the minimum

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difference in rating scale scores indicating an ecologically relevant effect is unknown. Thus, statistically significant though small effects on symptom scores may not equate to clinically relevant amelioration of difficulties in daily life[5]. The effects of pharmacological treatment on academic performance and quality of life in children and adolescents with ADHD appear to be low[6].

The administration of drugs such as methylphenidate almost certainly yields some short-term symptom reduction in children and adolescents with ADHD. However, the extent of therapeutic efficacy is unclear due to the low quality of outcome measures and possible bias of trials. The results of trials assessing efficacy and safety of ADHD medication over short time periods cannot be extrapolated to long-term outcomes. Long-term drug administration may result in a diminution of beneficial effects, since people with ADHD become more tolerant to the neurotransmitter alterations induced by medication[7]. The observations of pharmaco-epidemiological studies have suggested potential long-term benefits of medication for serious problems co-occurring with ADHD, such as substance abuse[8], transport accidents[9], criminal convictions[10] and suicidal behavior[11]. However, despite their substantial sample sizes, such observational population-based studies are vulnerable to many threats to validity and cannot account for all confounding variables possibly involved in the selection of people for treatment. The greatest threat to validity is differences in the indications for medication[5]. Randomized controlled trials, as the gold standard for measuring treatment effects, are required to address these issues. However, such trials supporting long-term effectiveness of psychostimulants for more than a few months are largely lacking[12]. The Multimodal Treatment Study of children with ADHD, the largest randomized controlled trial for ADHD so far conducted, involving 14 months of intensive administration of medication, behavior therapy or a combination of both, resulted in a substantial alleviation of symptoms and improvement of multiple aspects of functioning[13]. However, the differences between treatment groups at the end of the active treatment period had dissipated within two years post-treatment[14]. In addition, the children of all treatment groups continued to show substantial impairment in comparison with their classmates without ADHD at long term follow-up performed six and eight years after baseline[15]. It is therefore questionable whether the currently used treatments are capable of mitigating the negative impact of ADHD on quality of life over extended time periods.

Furthermore, little is known concerning the safety of extended administration of psychostimulants. A major concern regarding psychostimulant treatment in youths with a diagnosis of ADHD is a potential adverse effect on the developing brain, for example with respect to central dopaminergic functions[16-17]. The findings of long-term observations suggest that children with ADHD who were treated with psychostimulants into adulthood may present with a decrease in height as adults without any ongoing improvement in symptomatology[18]. Adverse effects of ADHD medications may also include serious cardiovascular events[19-21]. Possible risks of long-term administration of ADHD medication in adults have not been sufficiently explored[5]. Given the unproven long-term benefits of medications in ADHD and the risk of side effects[22-23], potential over-prescription and development of dependence or addiction[24], their value may be outweighed by their risks[5,12]. In summary, the evidence of the benefits and harms of methylphenidate in the treatment of ADHD is inconclusive[25].

The dearth of evidence supporting the ability of medications to address the broader daily needs of people with ADHD has led to a search for alternative management options. Various lifestyle factors, including diet and nutrition, have been proposed to be involved in the pathogenesis of the disorder and to be of potential value in its management[26-27]. Emerging evidence points to a role of nutrition in brain development and functioning. Furthermore, various nutrients and diet quality have been linked to behavioral, cognitive and affective functions as well as to the prevalence of mental disorders[27-30]. Nutritional deficiencies have been suggested to play a role in the pathophysiology and management of various mental disorders, such as depression, schizophrenia, autism spectrum disorder and ADHD[31-32]. Several kinds of dietary interventions, such as single micronutrient, multi-micronutrient and omega-3 fatty acid supplementation have therefore attracted increasing scientific interest[33].

In recent years, several articles have reviewed the available scientific literature on ADHD and food, diet and nutrition[31,33-41]. Certain nutrients, such as vitamins, minerals and polyunsaturated fatty acids[29,31,33], and dietary patterns, such as the Mediterranean diet[31], have been proposed to be helpful in the treatment of ADHD. Various studies have found a decrease in blood plasma concentrations of minerals, such as magnesium, zinc and iron, in children with ADHD at group level, and their supplementation may reduce ADHD symptoms in individuals with respective deficiencies. However, evidence in support of this is lacking[37]. The questions of whether vitamin deficiencies are involved in the pathophysiology of ADHD and whether vitamin supplements exert therapeutic effects also remain open[30]. The role of omega-3 fatty acids in the pathophysiology and therapy of ADHD is controversial[29,33]. Since blood levels of docosahexaenoic acid, eicosapentaenoic acid and arachidonic acid have been found to be significantly reduced in children with ADHD in comparison with controls, numerous clinical studies have examined the effects of omega-3 fatty acid supplementation on ADHD symptoms. However, systematic reviews of meta-analyses of double-blind placebo-controlled trials, in which ADHD symptoms were rated by parents and teachers, concluded that the effect sizes for supplementation of omega-3 fatty acids were small[42]. Furthermore, the pooling of the negative results of a more recent study with previous findings showed no overall effect of omega-3 fatty acids on ADHD symptoms[43]. Accordingly, there is currently little evidence to support the efficacy of omega-3 fatty acid supplementation in reducing the core symptoms of ADHD.

Despite the positive results reported by individual trials, no consistent finding of a significant decrease in ADHD symptoms for any kind of nutritional supplementation has been shown. There is therefore little support at present for the efficacy of single nutrients on the main symptoms of ADHD, and it appears unlikely that a single nutrient is capable of addressing all pathophysiological and clinical issues associated with a complex behavioral disorder such as ADHD. While subgroups of people with ADHD may benefit from the administration of micronutrients, supplementation above a certain threshold of micronutrient status may be ineffective. Moreover, since various comorbid psychiatric conditions are very common in individuals with ADHD, the efficacy of micronutrient supplements (or other nutrition-related interventions) may vary depending on the presence of comorbidities. Furthermore, the therapeutic efficacy of nutrients could be confined to critical time windows during the life span.

Potential adverse effects of long-term nutrient supplementation should also be considered[44]. In addition, the ill-defined nature of ADHD and the lack of biomarkers underpinning the concept of ADHD may hinder the identification of the role that nutrients and diets may play in the management of ADHD.

Recent investigations, instead of assessing the effects of single micronutrients in children with ADHD, have examined dietary patterns or whole diets. The role of dietary patterns in ADHD has been explored in several cross-sectional and case-control studies[36]. For example, the effects of a diet commonly assumed to be healthy (Mediterranean diet) on children and adolescents with newly diagnosed ADHD were examined in a case-control study[45]. Low adherence to the diet was positively associated with an elevated likelihood of ADHD diagnosis. Furthermore, a systematic review and meta-analysis of six dietary pattern studies has shown that a "healthy" dietary pattern (high in vegetables, fruits, seafood, polyunsaturated fatty acids, magnesium, zinc and phytochemicals) was associated with a significant decrease in the risk of ADHD, while "Western" (high in confectionery, red meat, refined grains, processed meats, fried potatoes, crisps, soft drinks, animal and hydrogenated fats) and "junk food" (large amounts of chocolate, biscuits, cakes, pizza, sweets, crisps and fizzy drinks) dietary patterns were associated with an elevated risk[46]. The findings of these observational studies emphasize a potential role of dietary patterns in ADHD. However, the observational study designs are unable to establish a causal relationship between diet and ADHD. For example, reverse causation, with ADHD behaviors leading to a preference for certain foods and diets, may explain the associations observed. The correlations between dietary habits and ADHD risk could also be caused by other factors, which were not recorded but were, in fact, the causal influences. For example, physical activity and lifestyle may correlate with dietary patterns and may be more important factors in ADHD symptomatology[26]. In addition, associations between adherence to healthy diets and low prevalence of ADHD do not necessarily imply protective effects of healthy foods consumed during childhood. The mothers of children consuming a healthy diet may also have adhered to healthy diets during pregnancy and have provided their children with essential nutritional compounds during critical phases of brain development.

Over many years, the most enduring proposal for an alternative treatment for ADHD has been the use of a food restriction or elimination diet. Such treatments involve the removal of certain foods from the diet in an effort to eliminate potential allergens contained naturally in food or in artificial ingredients with allergenic or toxic properties. Restricted elimination diets (also referred to as the few-foods diet or oligoantigenic diet) exclude from the diet food items to which a child shows hypersensitivity, indicated by an exacerbation of behavioral ADHD symptoms. This hypersensitivity may be allergic (immunoglobulin (Ig) E-mediated) or nonallergic. The idea of an elimination diet consisting of some hypoallergenic foods to improve behavior, mood or attention has attracted increased interest in recent years. The hypothesis that some children with ADHD may show sensitivity or allergic reactions to a variety of food items[47] has led to the development of the few-foods or oligoantigenic diet. Available evidence suggests that the investigation of the role of food hypersensitivities in ADHD is a promising avenue worthy of further exploration. The present review provides some historical aspects of the food allergy hypothesis and elimination diets in general as well as an update of recent developments regarding the few-foods diet in particular.

2. Food allergy hypothesis and elimination diets in ADHD

2.1 Early studies of food allergy and behavioral problems

As early as 1916, food allergy was suggested to be associated with disturbances of the nervous system, such as irritability, fretfulness, restlessness and sleeplessness[48]. In 1922, various "neuropathic" symptoms, including nervousness, peevishness, irritability, restlessness, sleep disturbances, unruliness and difficulties at school, were linked in children to food allergies[49]. These symptoms were claimed to be "not infrequently the result of irritation of the nervous system resulting from anaphylactic reactions to food proteins to which the patient has become sensitized"[49]. Cutaneous tests showed the presence of protein sensitization, most commonly to wheat, in all patients. An improvement or disappearance of the nervous symptoms was found following a specific therapy directed at the proteins to which the patients were sensitive, with dietary modification and elimination of the foods that tested positive[49]. Exclusion of foods and individualized elimination diets were also advised by others in the 1920s[50]. Several years later, Rowe[51] suggested that allergy to foods can cause psychological and emotional disturbances and was linked in childhood to restlessness, bursts of temper, incorrigibility, drowsiness, sullenness, somnolence, depression and significant changes in disposition. Schneider[52] believed that elimination diets could help improve these changes in behavior. With respect to the psychiatric evaluation of hyperkinetic children, it was noted that "too little attention is given by the general physician and pediatrician to the role of allergy"[52].

In 1947, food allergy was more specifically implicated in a range of behavioral problems in children[53]. Allergy to more than one food appeared to play a causative role in fatigue, irritability, crankiness and other behavioral abnormalities, such as sluggishness and depression, hyperkinesis and hyperexcitement as well as difficulty in concentration and impairment of memory. All of these behavioral symptoms hampered the schoolwork of affected children and disappeared when certain foods were removed from the diet[53]. While any food ingested was capable of causing chronic behavioral symptoms, sensitivity to wheat and corn was observed most frequently[53]. In 1954, three years before the term "hyperkinetic impulse disorder" was coined, many of the behavioral symptoms described above were summarized as "allergic tension-fatigue syndrome", with the two categories of "tension" (hyperkinesis and irritability) and "fatigue" (sluggishness and torpor). In contrast to psychosomatic approaches to allergy, somatic disease was proposed as a possible cause of behavioral and affective disorders rather than the effect. In pediatric practice in particular, the limited ability of children to articulate their symptoms may easily cause an organic basis of nervous manifestations to be overlooked. As a result, many children have received a diagnosis of mental disorder and have been prescribed psychiatric drugs rather than treatment for allergies[54].

By the 1950s, allergic reactions to foods and other substances were generally believed to be capable of triggering impairment of cerebral vascular function ("neuro-allergy"), which may cause migraine, epilepsy and behavioral abnormalities[55]. A survey conducted in 1950 found that many allergists in North America had observed allergy-induced character problems and personality changes which improved after elimination of the allergenic element[56]. A study published in 1961 reported that sensitivities to milk, eggs, cereals and chocolate were commonly seen in 50 children with hyperkinetic behavior, chronic fatigue, irritability and other symptoms[57]. However, only a minority of the children with food sensitivities were found to have positive skin-prick allergy test results for the foods identified by clinical assessment, which led to the conclusion that behavior-related food sensitivities can be revealed only through the administration of an oligoantigenic diet[57]. Orthodox allergists continued to accept the existence of a food allergy only if an immunological response could be elicited, for example by cutaneous prick testing. In contrast, unorthodox food allergists took the view that food allergy (or rather food intolerance) may not necessarily result in such a response and investigated a range of other reactions, including behavioral problems, which are presumed to be evoked by an idiosyncratic response to pharmacologically active food constituents[58]. Today, it remains unclear whether the presence of food allergy symptoms or positive skin-prick results increase the likelihood that elimination diets will ameliorate ADHD symptoms.

2.2 Feingold diet

In the 1970s, Feingold hypothesized that artificial food additives (colors and flavors) and foods rich in salicylates, which occur naturally in some foods, could play a role in the etiology of the hyperkinetic syndrome[59]. A study published in 1975 reported a rapid improvement in behavioral disturbances and learning abilities in children with hyperkinesis (or hyperactivity) and learning disabilities after dietary elimination of artificial food colorings and flavors as well as naturally occurring salicylates[59]. Favorable reports regarding children on this kind of dietary management were available from several countries, with almost 50% of children with hyperkinesis and learning disabilities responding to strict elimination diets. Feingold later viewed only artificial colorings and preservatives as causative of ADHD symptoms and adapted the diet accordingly. Preliminary results of a pilot group of 12 boys in a double-blind cross-over study validated the relationship of artificial colors and flavors with behavioral disturbances. Initial improvements observed following the Feingold (or Kaiser-Permanente) diet, eliminating artificial food colors and flavors, included a reduction of hyperactivity, impulsiveness and aggression, followed by improved gross and fine muscle coordination and subsequently by improved cognition and perception. The initial improvement in behavioral and mood patterns enabled the children to concentrate, which led to an increased attention span and better scholastic achievement. Cognitive and perceptive deficits did not improve unless a behavioral response to the diet was seen. Learning ability may improve slowly over extended periods of time[59]. From the mid-1970s, the validity of Feingold's hypothesis was tested repeatedly in various studies, with most trials randomly serving children food containing an additive that had been linked to hyperactive behavior and rating the children's behavioral response[60]. In a later double-blind crossover trial, the Feingold diet was compared with a control diet in 15 hyperkinetic children[61]. Standardized parent and teacher ratings following the control diet did not differ from baseline ratings performed for one month before treatment. In contrast, both parents and teachers observed fewer hyperkinetic symptoms on the Feingold diet in comparison with pretreatment ratings. While the teachers reported a highly significant alleviation of symptoms when the hyperkinetic children were receiving the Feingold diet as compared to the control condition, the parents did not[61]. Furthermore, a direct comparison of stimulant medication with the Feingold diet was conducted[62]. A total of 26 hyperactive children were randomly assigned to four treatment conditions. The participants received active or placebo medications combined with challenge cookies containing artificial food colors or control cookies without the additives. A cross-over design, including double-blind assessments with all children undergoing each of the four treatment conditions, was employed. Stimulant medication was more effective than diet in reducing hyperactive symptoms, as assessed using behavior checklists[62]. The parent and teacher ratings showed inconclusive diet effects. However, children receiving placebos showed greater hyperactive behaviors in the classroom when consuming cookies with artificial colors than when eating those without artificial additives. Depending on the criteria used, up to eight children showed diet-responsive behavior. Further research attempting to identify the subtypes of hyperactive children responsive to an artificial color-free diet has been suggested[62].

In summary, while some studies supported Feingold's hypothesis, others reported mixed or negative results. The main criticisms of the studies assessing the Feingold diet included poor experimental design, ambiguity in behavioral ratings, possible placebo effects and the fact that each study examined only one of thousands of food additives excluded from the Feingold diet. Most researchers investigating the Feingold diet concluded that more research was necessary. The majority of physicians took the view that the results of the available trials disproved the hypothesis and therefore declined to recommend the diet for the treatment of hyperactive children. By the mid-1980s, the Feingold diet had been marginalized in medical practice. However, many parents disregarded the results of randomized controlled trials in favor of direct observation, case studies and parental testimony and used the Feingold diet as a complementary or alternative treatment option. A critical discussion of the way in which the historical context as well as cultural, socioeconomic and political factors, rather than the scientific trials conducted, influenced the depiction of Feingold's theory can be found elsewhere[60].

2.3 Renewed interest in food additive elimination

Other elimination diet studies examining the effects of synthetic food additive elimination followed the Feingold trials. A large randomized controlled challenge study sparked renewed interest in the idea that food additives may trigger hyperactivity in children[63]. This study did not examine food elimination but challenged typically developing children with a beverage containing artificial food colors and a sodium benzoate preservative. The intake of food colors and/or sodium benzoate preservative resulted in increased hyperactivity in 3-year-old and 8/9-year-old children in the general population[63]. The findings of this study prompted the European Union Parliament

to require warning labels on foods containing certain colors. Furthermore, this study seemed to provide indirect support for the notion that elimination diets could help children with ADHD. In 2011, a qualitative review concluded that a subgroup of children with ADHD is sensitive to artificial color additives, flavors or salicylates and may benefit from a restriction or elimination diet[64]. This study emphasized differential responses among different children as well as the idea that elimination diets may be of value. Furthermore, children with attention deficit disorder who had responded to an elimination diet were challenged with foods in order to determine the cause of the worsening of their symptoms. While a wide range of foods provoked reactions, only a minority of children reacted primarily to artificial colorings[65]. In consequence, diets eliminating numerous foods and additives (oligoantigenic or few-foods diets) have attracted increasing interest.

3. Few-foods diet in ADHD

3.1 Strategy of elimination diets

Research using elimination diets to investigate food allergy/intolerance and behavior does not focus on specific food items but rather attempts to identify the individual foods to which a person might be sensitive. All elimination diets are empirical interventions encompassing two phases, during which symptoms are monitored while foods are eliminated and then reintroduced. In the first phase, the diet is administered for a given time period. If symptoms remit, foods or food additives are introduced one at a time in the second phase, during which the individual is observed for the possible return of symptoms. This phase is lengthy since many foods are required to be tested until a sufficient number of foods have been identified and a balanced diet without allergens can be established.

The specific content of diets eliminating certain foods in an attempt to diagnose and treat food allergies may vary, but three main forms of elimination diets can be distinguished: the first is a diet excluding a single suspected food (e.g. eggs), the second is a diet eliminating several foods containing the most common food allergens (wheat, eggs, milk and dairy products, soy, peanuts, seafood), and the third is a few-foods (or oligoantigenic) diet restricting dietary intake to a few less commonly consumed foods (e.g. lamb, venison, rice and others with low allergenic potential). The few-foods diet can identify multiple food allergies[66] and must be supervised by a qualified professional in order to avoid nutritional deficits. An overview of open-label, non-blind trials of restriction and elimination diets of any type (artificial color-free diet, few-foods diet and others) and their effects on symptom response rates in children with ADHD has been provided by others[67].

3.2 Controlled study of the few-foods diet

The first findings of a controlled study of the few-foods diet containing a limited variety of food items in hyperactive children were published in 1985[68]. The few-foods diet was administered for four weeks and consisted of two meats (e.g. lamb, chicken), two sources of carbohydrates (e.g. rice, potatoes), vegetable (e.g. any kind of brassica), two fruits (e.g. apple, banana), water, and multivitamin and calcium supplements. Of a total of 76 hyperactive children, the symptomatology of 62 (81%) improved significantly on the few-foods diet, with 21 presenting with a normal range of behavior. Twenty-eight of the children whose symptoms improved completed a placebo-controlled, double-blind, crossover trial, which sequentially re-introduced foods thought to provoke hyperactivity and associated symptoms. Symptoms were found to reappear much more frequently when the participants were on the active diet than on placebo. A total of 48 foods could be identified as adversely affecting the children's behavior, with colorants and preservatives (79%), soy (73%), cow's milk (64%), chocolate (59%), grapes (50%), wheat (49%) and oranges (45%) being the most common items provoking a reappearance of symptoms. None of the children were sensitive only to food colors and additives[68].

In a double-blind, placebo-controlled trial, a few-foods diet was examined in 49 hyperactive children. Twelve children (24%) responded to the diet, with the magnitude of response being similar to that of children receiving medication in the same trial[69]. The findings of this study suggest that the oligoantigenic diet is efficacious in some children with hyperactivity. Consequently, dietary intervention, including the few-foods diet, was recommended as an element of ADHD treatment protocols[70].

In the following years, the few-foods diet was implemented in several investigations. These studies demonstrated that an elimination diet can significantly reduce ADHD symptoms in children. For example, an open, descriptive study attempted to determine whether a standard elimination diet can reduce symptoms of ADHD in a heterogeneous group of young children[71]. Forty children with a diagnosis of ADHD followed their usual diet for two weeks and then consumed a few-foods elimination diet (turkey, rice, pear and lettuce) for a further two weeks. At the end of the elimination phase, parent ratings demonstrated an improvement in behavior in 25 children (62%) of at least 50% on symptom rating scales. Ten of 15 children (66%) with both parent and teacher ratings were found to show a significant decrease in symptoms both at home and in school[71].

Another large study aimed to investigate the connection between an elimination diet and behavior in an unselected group of children with ADHD[72]. In this double-blind crossover study, 100 children aged 4 to 8 years with ADHD were randomly assigned to an individually designed few-foods diet (N = 50) or to healthy diet counseling (N = 50). Children responding to the elimination diet were subsequently given a challenge using high-inflammatory or low-inflammatory foods on the basis of each child's individual IgG blood levels. Thirty children (60%) showed a positive response to the elimination diet, with 19 of 30 children (63%) experiencing a relapse of ADHD symptoms following the challenge foods, independent of their IgG blood test results. The authors concluded that their restricted elimination diet was effective for ADHD but that the use of IgG blood test to prescribe the diet was not useful[72]. The latter finding suggests that food intolerance rather than food allergy played a role in this population. However, a problem with these impressive findings was the reliance on the ratings of clinicians, who relied, in part, on information concerning behavior provided by parents who were not blind to the interventions.

3.3 Meta-analysis of few-foods diet trials

A systematic review of published meta-analyses including double-blind placebo-controlled trials of dietary interventions in children

with ADHD found that the average effect sizes ranged from 0.08 to 0.44 for artificial food color elimination and from 0.51 to 0.80 for the few-foods diet[42]. The effect sizes of artificial color elimination may be too small to contribute significantly to the therapy of ADHD treatment. However, the potential effects of an additives-free diet might be concealed by adverse reactions to other foods still contained in the diet. Therefore, more restricted diet interventions may be needed to produce greater behavioral effects. The effect sizes of the few-foods diet were found to be considerably larger than those for colorant elimination[42]. While this could be due to difficulties related to blinding, several few-foods studies received the maximum JADAD score for appropriate blinding[73]. Furthermore, the parental investment needed to apply a strenuous dietary intervention could underlie the relatively large effects. However, parental investment in various trials of the few-foods diet has been found to be marginal[65,68-69,74-75].

In contrast to the conclusions of previous reviews of diet and ADHD[67,76-77], the systematic review of published meta-analyses by Pelsser et al.[42] concluded that the evidence of beneficial effects of the few-foods diet on ADHD was convincing. This conclusion was based on effect sizes rather than *P*-values, as recommended, for example, by the American Psychological Association[78]. With respect to the interpretation of both single trials and meta-analyses, it is important to emphasize that the statistical significance of findings is not necessarily equivalent to clinical relevance, while statistical non-significance is not equivalent to clinical irrelevance[79-80]. The clinical relevance of an intervention may not be represented accurately when conclusions are based solely on statistical *P*-values[81-83]. For example, the information on statistical significance provided by *P*-values is highly dependent on sample sizes. Thus, changes from significant to insignificant outcomes or vice versa may result from (small) changes in sample size[79,83-84]. In contrast, effect sizes are largely unaffected by changes in sample size and therefore provide clinically relevant information[79,83-84]. Although effect sizes and confidence intervals are considered important in assessing the average clinical relevance of an intervention[85], *P*-values are frequently used as the decisive factor in accepting or rejecting outcomes in clinical studies and meta-analyses. Furthermore, the systematic review by Pelsser et al.[42] also included the first meta-analysis of few-foods diet trials[86], which was, according to the Scottish ADHD guidelines, of high quality with a very low risk of bias, providing the highest level of evidence[87]. However, the meta-analysis was not discussed in other previous reviews[67,76-77].

A summary of the results of meta-analyses of the few-foods diet in children with ADHD is presented in Table 1.

4. Recent studies of the few-foods diet in ADHD

In an uncontrolled, open-label dietary intervention study of a small sample of eight children aged 8 to 14 years with a diagnosis of ADHD according to ICD-10, food items which are commonly related to intolerances were eliminated for four weeks[91]. Five of eight children showed a significant symptom improvement of > 40% in the ADHD Rating Scale IV after the diet. In the following re-introduction phase lasting 8 to 16 weeks, nutrients with individual relevance to ADHD symptoms were identified. This study confirmed findings of previous research, with some people showing a significant improvement after 4 weeks of consuming a few-foods diet. In addition, the study demonstrated a high inter-rater reliability between a non-blinded child and adolescent psychiatrist and three blinded raters who evaluated ADHD Rating Scale IV scores in a pseudonymized video rating[91]. These results call for further randomized controlled trials.

A further study attempted to reveal how foods that may impact ADHD symptoms can be identified[92]. In this uncontrolled, open trial, 16 children with a diagnosis of ADHD were assessed before and after a restricted elimination diet. Participants kept a daily 24-h recall journal on nutrition and behavior and filled in the abbreviated Conners' scale to identify foods which increased ADHD symptoms.

Table 1
Meta-analyses of elimination diets in children with ADHD.

Authors	Focus of study	Studies included	Findings	Major limitations
Kavale and Forness[88]	Feingold diet	23 studies of varying quality	Effect size 0.11 (95% confidence interval (CI) = 0.045–0.191); Larger effect sizes associated with studies with low internal validity	Inclusion of uncontrolled studies
Schab and Trinh[89]	Artificial food colorings	15 double-blind, placebo-controlled studies	Overall effect size of artificial food colors on hyperactivity 0.28 (95% CI = 0.079–0.488), after exclusion of smallest and lowest quality trials 0.21 (95% CI = 0.007–0.414); Greatest effects in trials screening for responsiveness before enrollment	Use of unorthodox scales for behavioral response measurement; Clinical heterogeneity; Possible publication bias against small trials with negative results
Benton[86]	Elimination diets	5 well-designed studies	Effect size of food additives and intolerance on hyperactivity-related symptoms 0.80 (95% CI = 0.41–1.19)	
Nigg et al.[90]	Artificial food colorings	Feingold diet or other restriction diet eliminating synthetic color additives	Effect size of color additives on ADHD symptoms in high-quality studies 0.22 (95% CI = 0.10–0.41)	Lacking consistency in findings across information sources; Vulnerability to single study effects due to small number of studies and small aggregate sample
Nigg et al.[90]	Restriction/elimination diets	6 placebo-controlled diet challenge or crossover studies (N = 195)	Response rate of 41.5% (95% CI = 22%–64%), after removal of largest outlier 33% (95% CI = 19%–52%, N = 164)	
Sonuga-Barke et al.[73]	Artificial food color exclusion	8 randomized controlled trials	Effect size of artificial food color exclusion on ADHD symptoms 0.42 (95% CI = 0.13–0.70)	
Sonuga-Barke et al.[73]	Restriction/elimination diets	7 randomized controlled trials	Effect size of restricted elimination diets on ADHD symptoms 0.51 (95% CI = –0.02–1.04)	

After four weeks of elimination diet, the individual food sensitivities were identified in the re-introduction phase. A repetitive increase of ADHD symptoms by at least two points in the abbreviated Conners' scale after food introduction was found to hint at food sensitivity. Twenty-seven different foods, including milk and dairy product, grains and corn, were found to increase ADHD symptoms. Most participants showed sensitivities to more than one food[92]. The results suggest that the few-foods diet combined with subsequent food challenge is a valid method to identify individual food sensitivities in people with ADHD.

In order to examine the effect of a few-foods diet on physical complaints, such as headache, asthma, rhinitis as well as gastrointestinal and sleep problems, unpublished data from previously published studies have recently been analyzed[93]. Children with ADHD either followed a 5-week few-foods diet or received advice on healthy nutrition. A clinically relevant reduction for 10 of 21 complaints, as assessed using a physical complaint questionnaire, was found in the few-foods group compared to controls[93]. These findings need to be replicated in further trials.

In the Netherlands, the approach using the few-foods diet in children with ADHD is applied in practice. A retrospective study, including data from all children who started the few-foods approach in three specialized healthcare facilities during three consecutive months, has assessed the effectiveness of the few-foods approach in ADHD and oppositional defiant disorder in real life[94]. The findings of this study, including a total of 57 children, showed that the few-foods diet, administered in general practice by trained physicians for 5 weeks, may have clinically relevant effects on symptoms of ADHD and oppositional defiant disorder, both in children with and without medication for ADHD[94]. The use of medication was significantly reduced in responders to the few-foods diet. Using this diet in practice may result in secondary prevention of ADHD.

A recent open study without control group investigated the long-term effects of a few-foods diet on ADHD symptoms[95]. Twenty-eight children and adolescents aged 7 to 14 years with a diagnosis of ADHD according to the criteria of DSM-IV and ICD-10 received a few-foods diet for 4 weeks. Twenty-one participants were re-assessed after 3.5 years[95]. Fourteen of these participants fulfilled the responder criterion. In comparison with the baseline before the dietary intervention, the mean ADHD Rating Scale IV score showed a significant improvement not only immediately after commencing the diet, but also at follow-up 3.5 years later[95]. These results suggest that individually adjusted nutrition may offer a long-term improvement of ADHD symptoms. However, it remains unclear which factors (e.g. strictness of long-term adherence to the diet) may contribute to beneficial effects over extended periods of time. Furthermore, the small sample size of this study and the lack of blinding and control group are issues to be addressed in future studies.

The mechanisms underlying the reduction in ADHD symptoms following a few-foods diet are unknown. An open-label intervention study examined whether behavioral changes after a few-foods diet are associated with altered brain function during inhibitory control in 79 boys aged 8 to 10 years with ADHD[96]. According to parents' ADHD rating before and after the few-foods diet, 50 of 79 participants (63%) were diet responders, showing a reduction of ADHD symptoms of at least 40%. Functional magnetic resonance imaging was performed during a stop-signal task before and after the few-foods diet. Region-of-interest analyses found that activation in brain regions implicated in the stop-signal task was not associated with changes in ADHD symptoms. However, whole-brain analyses demonstrated a correlation between the decrease in ADHD symptoms and an increase in precuneus activation[96]. These findings suggest that a neurocognitive mechanism may be involved in the effects of the few-foods diet in children with ADHD.

5. Future directions

A growing body of evidence suggests that subgroups of children and adolescents with ADHD may benefit from the elimination of certain foods. A major advantage of the few-foods diet is that it can be tailored to the individual. The high response rate to this diet, of over 50% reported in uncontrolled studies, indicates an important role of food intolerances in the pathophysiology of ADHD. This promising personalized nutrition-based approach to the management of ADHD deserves further systematic investigation and should be considered in all children with ADHD. Individual nutritional recommendations on the basis of the elimination of certain food items may become an additional therapeutic option. However, unequivocal recommendation of the few-foods diet for children with ADHD requires further large-scale trials with children who are not selected on the basis of previous reaction to foods and whose behavior ratings are truly blind to treatment. Implementing the few-foods diet can be a major challenge for both clinicians and families. Discipline is required to maintain strict adherence to the diet, involving major changes in food intake and exclusion of highly palatable foods. This may lead to conflict between children and parents. Moreover, the few-foods diet must be supervised by a dietitian to ensure nutritional adequacy.

The medium-to-large effect sizes found for the few-foods diet, together with the reduction of heterogeneity resulting from subgroup analyses, suggest the value of this dietary approach in children with ADHD[42]. However, the few-foods diet is a short-term diagnostic tool to identify diet-sensitive children rather than a long-term treatment. The actual treatment consists of a diet individually tailored on the basis of repeated food challenges determining the food items to be avoided. The burdensome development of a personalized dietary plan may take several months and is feasible in motivated families only[97]. Large-scale implementation of the few-foods approach may therefore be unrealistic. Further trials should include information concerning the prevalence of comorbid disorders and the ways in which they are affected by the diet.

Quantitative measurement of ADHD-related functions, for example using neuropsychological tests, has been found to be sensitive to change following intervention[98-99]. However, while various tests assessing cognitive functions allow blinded measurement, neuropsychological testing does not seem to provide markers of ADHD[100]. Furthermore, the ecological validity of cognitive tests in clinical assessment is open to question[101]. Therefore, intervention studies in children with ADHD rely mainly on behavioral monitoring by parents and teachers. While parents are in many ways ideally suited to assess changes in their child's behavior, it is difficult to blind them to dietary elimination. Therefore, individuals who can maintain blindness, such as teachers or independent observers in the classroom, should be used[63,102]. Dietary intervention studies commonly use multiple informants and assessment scales. Therefore, pre-trial

study registration specifying the primary outcomes is required to avoid outcome selection bias[103]. Trial registration can also reduce publication bias, since failure to make the results of clinical trials available has been found to be common[104].

Future research should also attempt to elucidate the biological mechanisms underlying the effects of the few-foods diet. These may include inflammatory processes and biomarkers as well as the gut microbiota, the enteric nervous system and the gut-brain axis[105-106]. Ascertaining biological mechanisms and pathways may lead to simpler diagnostic procedures capable of distinguishing between diet responders and nonresponders.

6. Conclusion

The rationale of the few-foods diet is to eliminate certain foods from the diet in order to exclude potential allergens contained either naturally in food or in artificial ingredients with allergenic properties. The few-foods diet is a diagnostic tool that attempts to identify individual foods to which a person might be sensitive. Based on randomized controlled assessment, the effect sizes of diets free of artificial colors have been found to be small to medium and those of polyunsaturated fatty acid supplementation negligible to small. These dietary interventions are therefore unlikely to provide a tangible contribution to the treatment of children with ADHD. In contrast, the effect sizes of the few-foods diet have been shown to be medium to large, which justifies its diagnostic use. Thus, the few-foods diet may provide novel personalized options for the management of ADHD. Elucidating the mechanisms underlying the effects of food in ADHD may result in a less demanding procedure to identify those responsive to the few-foods diet.

The few-foods diet can be very useful for identifying intolerance to multiple foods in individual children with ADHD. A major limitation of the available literature on the few-foods diet in ADHD is the small database. Properly controlled studies have so far examined only a few hundred children with ADHD. However, on the basis of double-blind placebo-controlled evidence, the effect sizes of a few-foods diet in children with ADHD have been shown to be medium to large. Even small average effect sizes in clinical terms would be relevant from the perspective of population-wide prevention efforts. This appears to justify the implementation of a diagnostic few-foods diet in children with ADHD and may offer innovative therapeutic approaches in subgroups of children with ADHD. In addition, preliminary evidence not based on randomized controlled assessment suggests that individually adjusted nutrition may offer a long-term improvement of ADHD symptoms. Further large-scale, randomized controlled studies conducted in unselected children including assessment of long-term outcome are warranted.

Since food intolerances are individual, the few-foods diet is currently the best approach to identify them. Personalized nutrition could be a valid approach to the individualized treatment of ADHD. In the diagnostic process and in treatment approaches to ADHD, pediatricians and child psychiatrists should give greater consideration to exposure to foods and other environmental factors. The available evidence suggests that exposure to foods and hypersensitive mechanisms can play an important role in the multifactorial etiology of ADHD. The results of the clinical studies conducted so far are encouraging and support the future use of the few-foods diet. The findings should be considered in both the diagnosis and treatment of ADHD in clinical practice.

The interrelationship between basic nutrition and food reactivity requires further investigation. A modified diet may also be beneficial in terms of nutritional content. Optimizing nutrition while eliminating potential food intolerances or allergies may be able to include the beneficial effects of healthy dietary patterns, such as the Mediterranean diet, in the management of ADHD.

Conflict of interest

Klaus W. Lange is a scientific editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare there is no conflict of interest.

References

[1] A. Thapar, M. Cooper, Attention deficit hyperactivity disorder, Lancet 387 (2016) 1240-1250. https://doi.org/10.1016/S0140-6736(15)00238-X.

[2] C.M. Jensen, H.C. Steinhausen, Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study, Atten. Defic. Hyperact. Disord. 7 (2015) 27-38. https://doi.org/10.1007/s12402-014-0142-1.

[3] B. Wankerl, J. Hauser, E. Makulska-Gertruda, et al., Neurobiologische Grundlagen der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, Fortschr. Neurol. Psychiatr. 82 (2014) 9-29. https://doi.org/10.1055/s-0033-1355710.

[4] J. Thome, A.C. Ehlis, A.J. Fallgatter, et al., Biomarkers for attention-deficit/hyperactivity disorder (ADHD). A consensus report of the WFSBP task force on biological markers and the World Federation of ADHD, World J. Biol. Psychiatry 13 (2012) 379-400. https://doi.org/10.3109/15622975.2012.690535.

[5] K.W. Lange, The treatment of attention deficit hyperactivity disorder has no proven long-term benefits but possible adverse effects, Mov. Nutr. Health Dis. 1 (2017) 11-25. https://doi.org/10.5283/mnhd.4.

[6] A.F. Kortekaas-Rijlaarsdam, M. Luman, E. Sonuga-Barke, et al., Does methylphenidate improve academic performance? A systematic review and meta-analysis, Eur. Child Adolesc. Psychiatry 28 (2019) 155-164. https://doi.org/10.1007/s00787-018-1106-3.

[7] G.J. Wang, N.D. Volkow, T. Wigal, et al., Long-term stimulant treatment affects brain dopamine transporter level in patients with attention deficit hyperactive disorder, PLoS ONE 8 (2013) e63023. https://doi.org/10.1371/journal.pone.0063023.

[8] Z. Chang, P. Lichtenstein, L. Halldner, et al., Stimulant ADHD medication and risk for substance abuse, J. Child Psychol. Psychiatry 55 (2014) 878-885. https://doi.org/10.1111/jcpp.12164.

[9] Z. Chang, P. Lichtenstein, B.M. D'Onofrio, et al., Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study, JAMA Psychiatry 71 (2014) 319-325. https://doi.org/10.1001/jamapsychiatry.2013.4174.

[10] P. Lichtenstein, L. Halldner, J. Zetterqvist, et al., Medication for attention deficit-hyperactivity disorder and criminality, N. Engl. J. Med. 367 (2012) 2006-2014. https://doi.org/10.1056/NEJMoa1203241.

[11] Q. Chen, A. Sjölander, B. Runeson, et al., Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study, BMJ 348 (2014) g3769. https://doi.org/10.1136/bmj.g3769.

[12] O.J. Storebø, E. Faltinsen, M. Zwi, et al., The jury is still out on the benefits and harms of methylphenidate for children and adolescents with Attention-Deficit/Hyperactivity Disorder, Clin. Pharmacol. Ther. 104 (2018) 606-609. https://doi.org/10.1002/cpt.1149.

[13] MTA Cooperative Group, A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder, Arch. Gen. Psychiatry 56 (1999) 1073-1086. https://doi.org/10.1001/archpsyc.56.12.1073.

[14] P.S. Jensen, L.E. Arnold, J.M. Swanson, et al., 3-Year follow-up of the NIMH MTA study, J. Am. Acad. Child Adolesc. Psychiatry 46 (2007) 989-1002. https://doi.org/10.1097/CHI.0b013e3180686d48.

[15] B.S.G. Molina, S.P. Hinshaw, J.M. Swanson, et al., The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study, J. Am. Acad. Child Adolesc. Psychiatry 48 (2009) 484-500. https://doi.org/10.1097/CHI.0b013e31819c23d0.

[16] Y.S. Huang, M.H. Tsai, Long-term outcomes with medications for attention-deficit hyperactivity disorder: current status of knowledge, CNS Drugs 25 (2011) 539-554. https://doi.org/10.2165/11589380-000000000-00000.
[17] N.D. Volkow, T.R. Insel, What are the long-term effects of methylphenidate treatment?, Biol. Psychiatry 54 (2003) 1307-1309. https://doi.org/10.1016/j.biopsych.2003.10.019.
[18] J.M. Swanson, L.E. Arnold, B.S.G. Molina, et al., Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression, J. Child Psychol. Psychiatry 58 (2017) 663-678. https://doi.org/10.1111/jcpp.12684.
[19] J. Sieluk, B. Palasik, S. dosReis, et al., ADHD medications and cardiovascular adverse events in children and adolescents: cross-national comparison of risk communication in drug labeling, Pharmacoepidemiol. Drug Saf. 26 (2017) 274-284. https://doi.org/10.1002/pds.4164.
[20] L. Hennissen, M.J. Bakker, T. Banaschewski, et al., Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD: a systematic review and meta-analysis of trials of methylphenidate, amphetamines and atomoxetine, CNS Drugs 31 (2017) 199-215. https://doi.org/10.1007/s40263-017-0410-7.
[21] J.W. Jackson, The cardiovascular safety of methylphenidate, BMJ 353 (2016) i2874. https://doi.org/10.1136/bmj.i2874.
[22] I. Singh, Beyond polemics: science and ethics of ADHD, Nat. Rev. Neurosci. 9 (2008) 957-964. https://doi.org/10.1038/nrn2514.
[23] J. Graham, D. Coghill, Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management, CNS Drugs 22 (2008) 213-237. https://doi.org/10.2165/00023210-200822030-00003.
[24] T.M. Winhusen, D.F. Lewis, P.D. Riggs, et al., Subjective effects, misuse, and adverse effects of osmotic-release methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder, J. Child Adolesc. Psychopharmacol. 21 (2011) 455-463. https://doi.org/10.1089/cap.2011.0014.
[25] K.W. Lange, The evidence of the benefits and harms of methylphenidate in the treatment of attention deficit/hyperactivity disorder is inconclusive, J. Pharmacol. Clin. Toxicol. 6 (2018) 1118.
[26] K.W. Lange, Lifestyle and attention deficit/hyperactivity disorder, Mov. Nutr. Health Dis. 2 (2018) 22-30. https://doi.org/10.5283/mnhd.10.
[27] K.W. Lange, Diet, exercise, and mental disorders - public health challenges of the future, Mov. Nutr. Health Dis. 2 (2018) 39-59. https://doi.org/10.5283/MNHD.12.
[28] W. Marx, G. Moseley, M. Berk, et al., Nutritional psychiatry: the present state of the evidence, Proc. Nutr. Soc. 76 (2017) 427-436. https://doi.org/10.1017/S0029665117002026.
[29] K.W. Lange, Omega-3 fatty acids and mental health, Glob. Health J. 4 (2020) 18-30. https://doi.org/10.1016/j.glohj.2020.01.004.
[30] K.W. Lange, Dietary factors in the etiology and therapy of attention deficit/hyperactivity disorder, Curr. Opin. Clin. Nutr. Metab. Care 20 (2017) 464-469. https://doi.org/10.1097/MCO.0000000000000415.
[31] K.W. Lange, Micronutrients and diets in the treatment of attention-deficit/hyperactivity disorder: chances and pitfalls, Front. Psychiatry 11 (2020) 102. https://doi.org/10.3389/fpsyt.2020.00102.
[32] J. Sarris, A.C. Logan, T.N. Akbaraly, et al., Nutritional medicine as mainstream in psychiatry, Lancet Psychiatry 2 (2015) 271-274. https://doi.org/10.1016/S2215-0366(14)00051-0.
[33] K.W. Lange, Do food bioactives play a role in attention-deficit/ hyperactivity disorder? J. Food Bioact. 4 (2018) 1-7. https://doi.org/10.31665/JFB.2018.4160.
[34] K.W. Lange, Hyperactivity: nutritional aspects, in: B. Caballero (Ed.), Encyclopedia of human nutrition, fourth ed. third vol., Elsevier, 2023, pp. 353-360. https://doi.org/10.1016/B978-0-12-821848-8.00065-2.
[35] N.M. Uldall Torp, P.H. Thomsen, The use of diet interventions to treat symptoms of ADHD in children and adolescents - a systematic review of randomized controlled trials, Nord. J. Psychiatry 74 (2020) 558-568. https://doi.org/10.1080/08039488.2020.1769187.
[36] K.W. Lange, Y. Nakamura, A. Reissmann, Diet and food in attention-deficit hyperactivity disorder, J. Future Foods 2 (2022) 112-118. https://doi.org/10.1016/j.jfutfo.2022.03.008.
[37] K.W. Lange, J. Hauser, K.M. Lange, et al., The role of nutritional supplements in the treatment of ADHD: what the evidence says? Curr. Psychiatry Rep. 19 (2017) 8. https://doi.org/10.1007/s11920-017-0762-1.
[38] K.W. Lange, K.M. Lange, Y. Nakamura, et al., Nutrition in the management of ADHD: a review of recent research. Curr. Nutr. Rep. 12 (2023).
[39] A. Farsad-Naeimi, F. Asjodi, M. Omidian, et al., Sugar consumption, sugar sweetened beverages and attention deficit hyperactivity disorder: a systematic review and meta-analysis, Complement. Ther. Med. 53 (2020) 102512. https://doi.org/10.1016/j.ctim.2020.102512.
[40] B. Del-Ponte, G.C. Quinte, S. Cruz, et al., Dietary patterns and attention deficit/hyperactivity disorder (ADHD): a systematic review and meta-analysis, J. Affect. Disord. 252 (2019) 160-173. https://doi.org/10.1016/j.jad.2019.04.061.
[41] V. Breda, R.O. Cerqueira, G. Ceolin, et al., Is there a place for dietetic interventions in adult ADHD?, Prog. Neuropsychopharmacol. Biol. Psychiatry 119 (2022) 110613. https://doi.org/10.1016/j.pnpbp.2022.110613.
[42] L.M. Pelsser, K. Frankena, J. Toorman, et al., Diet and ADHD, reviewing the evidence: a systematic review of meta-analyses of double-blind placebo-controlled trials evaluating the efficacy of diet interventions on the behavior of children with ADHD, PLoS ONE 12 (2017) e0169277. https://doi.org/10.1371/journal.pone.0169277.
[43] C. Cornu, C. Mercier, T. Ginhoux, et al., A double-blind placebo-controlled randomised trial of omega-3 supplementation in children with moderate ADHD symptoms, Eur. Child Adolesc. Psychiatry 27 (2018) 377-384. https://doi.org/10.1007/s00787-017-1058-z.
[44] K.W. Lange, Y. Nakamura, A.M. Gosslau, et al., Are there serious adverse effects of omega-3 polyunsaturated fatty acid supplements?, J. Food Bioact. 7 (2019) 1-6. https://doi.org/10.31665/JFB.2019.7192.
[45] A. Rios-Hernandez, J.A. Alda, A. Farran-Codina, et al., The mediterranean diet and ADHD in children and adolescents, Pediatrics 139 (2017) e20162027. https://doi.org/10.1542/peds.2016-2027.
[46] E. Shareghfarid, Z.S. Sangsefidi, A. Salehi-Abargouei, et al., Empirically derived dietary patterns and food groups intake in relation with Attention Deficit/Hyperactivity Disorder (ADHD): a systematic review and meta-analysis, Clin. Nutr. ESPEN 36 (2020) 28-35. https://doi.org/10.1016/j.clnesp.2019.10.013.
[47] L.M.J. Pelsser, J.K. Buitelaar, H.F.J. Savelkoul, ADHD as a (non) allergic hypersensitivity disorder: a hypothesis, Pediatr. Allergy Immunol. 20 (2009) 107-112. https://doi.org/10.1111/j.1399-3038.2008.00749.x.
[48] B.R. Hoobler, Some early symptoms suggesting protein sensitization in infancy, Am. J. Dis. Child. 12 (1916) 129-135. https://doi.org/10.1001/ARCHPEDI.1916.04110140022003.
[49] W.R. Shannon, Neuropathic manifestations in infants and children as a result of anaphylactic reaction to foods contained in their dietary, Am. J. Dis. Child. 24 (1922) 89-94. https://doi.org/10.1001/ARCHPEDI.1922.04120070092008.
[50] G. Piness, H. Miller, Allergic manifestations in infancy and childhood, Arch. Pediatr. 42 (1925) 557-562.
[51] A.H. Rowe, Food allergy, its manifestations, diagnosis, and treatment with a general discussion of bronchial asthma, Lea & Febiger, Philadelphia, 1931.
[52] W.F. Schneider, Psychiatric evaluation of the hyperkinetic child, J. Pediatr. 26 (1945) 559-570. https://doi.org/10.1016/S0022-3476(45)80083-5.
[53] T.G. Randolph, Allergy as a causative factor of fatigue, irritability, and behavior problems of children, J. Pediatr. 31 (1947) 560–572. https://doi.org/10.1016/s0022-3476(47)80145-3.
[54] F. Speer, The allergic tension-fatigue syndrome, Pediatr. Clin. North Am. (1954) 1029-1037. https://doi.org/10.1016/s0031-3955(16)30167-5.
[55] T.W. Clarke, Neuro-allergy in childhood, N. Y. State J. Med. 48 (1948) 393-397.
[56] T.W. Clarke, The relation of allergy to character problems in children, Ann. Allergy 8 (1950) 175-187.
[57] W.G. Crook, W.W. Harrison, S.E. Crawford, et al., Systemic manifestations due to allergy. Report of fifty patients and a review of the literature on the subject (sometimes referred to as allergic toxemia and the allergic tension-fatigue syndrome), Pediatrics 27 (1961) 790-799.
[58] T.G. Randolph, R.W. Moss, An alternative approach to allergies: the new field of clinical ecology unravels the environmental causes of mental and physical ills, Lippincott & Crowell, New York, 1980.
[59] B.F. Feingold, Hyperkinesis and learning disabilities linked to artificial food flavors and colors, Am. J. Nurs. 75 (1975) 797-803.
[60] M. Smith, An alternative history of hyperactivity: food additives and the Feingold diet, Rutgers University Press, New Brunswick, NJ, 2011.
[61] C.K. Conners, C.M. Goyette, D.A. Southwick, et al., Food additives and hyperkinesis: A controlled double-blind study, Pediatrics 58 (1976) 154-166.
[62] J.I. Williams, D.M. Cram, F.T. Tausig, et al., Relative effects of drugs and diet on hyperactive behaviors: an experimental study, Pediatrics (1978) 811-817.
[63] D. McCann, A. Barrett, A. Cooper, et al., Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial, Lancet 370 (2007) 1560-1567. https://doi.org/10.1016/S0140-6736(07)61306-3.
[64] L.J. Stevens, T. Kuczek, J.R. Burgess, et al., Dietary sensitivities and ADHD symptoms: thirty-five years of research, Clin. Pediatr. 50 (2011) 279-293. https://doi.org/10.1177/0009922810384728.

[65] C.M. Carter, M. Urbanowicz, R. Hemsley, et al., Effects of a few food diet in attention deficit disorder, Arch. Dis. Child. 69 (1993) 564-568. https://doi.org/10.1136/adc.69.5.564.
[66] K.E.C. Grimshaw, Dietary management of food allergy in children, Proc. Nutr. Soc. 65 (2006) 412-417. https://doi.org/10.1017/s0029665106005167.
[67] J.T. Nigg, K. Holton, Restriction and elimination diets in ADHD treatment, Child Adolesc. Psychiatr. Clin. N. Am. 23 (2014) 937-953. https://doi.org/10.1016/j.chc.2014.05.010.
[68] J. Egger, C.M. Carter, P.J. Graham, et al., Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome, Lancet 1 (1985) 540-545. https://doi.org/10.1016/s0140-6736(85)91206-1.
[69] M.H. Schmidt, P. Möcks, B. Lay, et al., Does oligoantigenic diet influence hyperactive/conduct-disordered children-a controlled trial, Eur. Child Adolesc. Psychiatry 6 (1997) 88-95. https://doi.org/10.1007/BF00566671.
[70] R. Schnoll, D. Burshteyn, J. Cea-Aravena, Nutrition in the treatment of attention-deficit hyperactivity disorder: a neglected but important aspect, Appl. Psychophysiol. Biofeedback 28 (2003) 63-75. https://doi.org/10.1023/a:1022321017467.
[71] L.M.J. Pelsser, J.K. Buitelaar, Gunstige invloed van een standaardeliminatiedieet op het gedrag van jonge kinderen met aandachtstekort-hyperactiviteitstoornis (ADHD), Ned. Tijdschr. Geneeskd. 146 (2002) 2543-2547.
[72] L.M. Pelsser, K. Frankena, J. Toorman, et al., Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial, Lancet 377 (2011) 494-503. https://doi.org/10.1016/S0140-6736(10)62227-1.
[73] E.J.S. Sonuga-Barke, D. Brandeis, S. Cortese, et al., Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments, Am. J. Psychiatry 170 (2013) 275-289. https://doi.org/10.1176/appi.ajp.2012.12070991.
[74] B.J. Kaplan, J. McNicol, R.A. Conte, et al., Dietary replacement in preschool-aged hyperactive boys, Pediatrics 83 (1989) 7-17.
[75] M. Boris, F.S. Mandel, Foods and additives are common causes of the attention deficit hyperactive disorder in children, Ann. Allergy 72 (1994) 462-468.
[76] J. Stevenson, J. Buitelaar, S. Cortese, et al., Research review: the role of diet in the treatment of attention-deficit/hyperactivity disorder--an appraisal of the evidence on efficacy and recommendations on the design of future studies, J. Child Psychol. Psychiatry 55 (2014) 416-427. https://doi.org/10.1111/jcpp.12215.
[77] M.J. Heilskov Rytter, L.B.B. Andersen, T. Houmann, et al., Diet in the treatment of ADHD in children - a systematic review of the literature, Nord. J. Psychiatry 69 (2015) 1-18. https://doi.org/10.3109/08039488.2014.921933.
[78] American Psychological Association, Publication manual of the American Psychological Association, sixth ed., American Psychological Association, Washington, DC, 2010.
[79] C.J. Dunst, D.W. Hamby, Guide for calculating and interpreting effect sizes and confidence intervals in intellectual and developmental disability research studies, J. Intellect. Dev. Disabil. 37 (2012) 89-99. https://doi.org/10.3109/13668250.2012.673575.
[80] M. Coulson, M. Healey, F. Fidler, et al., Confidence intervals permit, but do not guarantee, better inference than statistical significance testing, Front. Psychol. 1 (2010) 26. https://doi.org/10.3389/fpsyg.2010.00026.
[81] R. Hubbard, R.M. Lindsay, Why *P* values are not a useful measure of evidence in statistical significance testing, Theory Psychol. 18 (2008) 69-88. https://doi.org/10.1177/0959354307086923.
[82] S. Goodman, A dirty dozen: twelve *P*-value misconceptions, Semin. Hematol. 45 (2008) 135-140. https://doi.org/10.1053/j.seminhematol.2008.04.003.
[83] J.A. Durlak, How to select, calculate, and interpret effect sizes, J. Pediatr. Psychol. 34 (2009) 917-928. https://doi.org/10.1093/jpepsy/jsp004.
[84] C.O. Fritz, P.E. Morris, J.J. Richler, Effect size estimates: current use, calculations, and interpretation, J. Exp. Psychol. Gen. 141 (2012) 2-18. https://doi.org/10.1037/a0024338.
[85] J.P. Higgins, S. Green, Cochrane handbook for systematic reviews of interventions version 5.1.0, The Cochrane Collaboration, 2011.
[86] D. Benton, The impact of diet on anti-social, violent and criminal behaviour, Neurosci. Biobehav. Rev. 31 (2007) 752-774. https://doi.org/10.1016/j.neubiorev.2007.02.002.
[87] Scottish Intercollegiate Guidelines Network, Management of attention deficit and hyperkinetic disorders in children and young people, SIGN, Edinburgh, 2009.
[88] K.A. Kavale, S.R. Forness, Hyperactivity and diet treatment: a meta-analysis of the Feingold hypothesis, J. Learn. Disabil. 16 (1983) 324-330. https://doi.org/10.1177/002221948301600604.
[89] D.W. Schab, N.H.T. Trinh, Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials, J. Dev. Behav. Pediatr. 25 (2004) 423-434. https://doi.org/10.1097/00004703-200412000-00007.
[90] J.T. Nigg, K. Lewis, T. Edinger, et al., Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives, J. Am. Acad. Child Adolesc. Psychiatry 51 (2012) 86-97. https://doi.org/10.1016/j.jaac.2011.10.015.
[91] A. Dölp, K. Schneider-Momm, P. Heiser, et al., Oligoantigenic diet improves children's ADHD rating scale scores reliably in added video-rating, Front. Psychiatry 11 (2020) 730. https://doi.org/10.3389/fpsyt.2020.00730.
[92] E. Yorgidis, L. Beiner, N. Blazynski, et al., Individual behavioral reactions in the context of food sensitivities in children with attention-deficit/hyperactivity disorder before and after an oligoantigenic diet, Nutrients 13 (2021) 2598. https://doi.org/10.3390/nu13082598.
[93] L. Pelsser, T. Stobernack, K. Frankena, Physical complaints decrease after following a few-foods diet in children with ADHD, Nutrients 14 (2022) 3036. https://doi.org/10.3390/nu14153036.
[94] L. Pelsser, K. Frankena, J. Toorman, et al., Retrospective outcome monitoring of ADHD and nutrition (ROMAN): The effectiveness of the few-foods diet in general practice, Front. Psychiatry 11 (2020) 96. https://doi.org/10.3389/fpsyt.2020.00096.
[95] G. Walz, N. Blazynski, L. Frey, et al., Long-term effects of an oligoantigenic diet in children with attention-deficit/hyperactivity disorder (ADHD) on core symptomatology, Nutrients 14 (2022) 5111. https://doi.org/10.3390/nu14235111.
[96] S. Hontelez, T. Stobernack, L.M. Pelsser, et al., Correlation between brain function and ADHD symptom changes in children with ADHD following a few-foods diet: an open-label intervention trial, Sci. Rep. 11 (2021) 22205. https://doi.org/10.1038/s41598-021-01684-7.
[97] L.M. Pelsser, D.J. van Steijn, K. Frankena, et al., A randomized controlled pilot study into the effects of a restricted elimination diet on family structure in families with ADHD and ODD, Child Adolesc. Ment. Health 18 (2013) 39-45. https://doi.org/10.1111/j.1475-3588.2012.00652.x.
[98] C.L. Huang-Pollock, S.L. Karalunas, H. Tam, et al., Evaluating vigilance deficits in ADHD: a meta-analysis of CPT performance, J. Abnorm. Psychol. 121 (2012) 360-371. https://doi.org/10.1037/a0027205.
[99] R. Lambek, R. Tannock, S. Dalsgaard, et al., Executive dysfunction in school-age children with ADHD, J. Atten. Disord. 15 (2011) 646-655. https://doi.org/10.1177/1087054710370935.
[100] K.W. Lange, J. Hauser, K.M. Lange, et al., Utility of cognitive neuropsychological assessment in attention-deficit/hyperactivity disorder, Atten. Defic. Hyperact. Disord. 6 (2014) 241-248. https://doi.org/10.1007/s12402-014-0132-3.
[101] K.W. Lange, O.L. Bock, Ökologische Validität klinischer Testverfahren in der kognitiven und motorischen Rehabilitation, in: P. Frommelt, A. Thöne-Otto, H. Grötzbach (Eds.), NeuroRehabilitation, Springer, 2023.
[102] H.B. Abikoff, P.S. Jensen, L.L.E. Arnold, et al., Observed classroom behavior of children with ADHD: relationship to gender and comorbidity, J. Abnorm. Child Psychol. 30 (2002) 349-359. https://doi.org/10.1023/a:1015713807297.
[103] A.W. Chan, D.G. Altman, Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors, BMJ 330 (2005) 753. https://doi.org/10.1136/bmj.38356.424606.8F.
[104] T. Shamliyan, R.L. Kane, Clinical research involving children: registration, completeness, and publication, Pediatrics 129 (2012) e1291-1300. https://doi.org/10.1542/peds.2010-2847.
[105] L.A. David, C.F. Maurice, R.N. Carmody, et al., Diet rapidly and reproducibly alters the human gut microbiome, Nature 505 (2014) 559-563. https://doi.org/10.1038/nature12820.
[106] S.M. Collins, M. Surette, P. Bercik, The interplay between the intestinal microbiota and the brain, Nat. Rev. Microbiol. 10 (2012) 735-742. https://doi.org/10.1038/nrmicro2876.