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The Role of Nutritional Supplements in the Treatment of ADHD: What the Evidence Says

Klaus W. Lange[1] · Joachim Hauser[1] · Katharina M. Lange[1] · Ewelina Makulska-Gertruda[1] · Yukiko Nakamura[1] · Andreas Reissmann[1] · Yuko Sakaue[2] · Tomoyuki Takano[3] · Yoshihiro Takeuchi[2]

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Abstract Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder in children and adolescents and may persist into adulthood. Insufficient nutritional supply of long-chain polyunsaturated fatty acids (LC-PUFAs) and other components including various minerals has been suggested to play a role in the development of ADHD symptoms. This review presents the evidence regarding the role of nutritional PUFA, zinc, iron, and magnesium supplements in the treatment of ADHD with a focus on the critical evaluation of the relevant literature published from 2014 to April 2016. The evaluation of therapeutic nutritional LC-PUFA supplementation in ADHD has shown mixed and inconclusive results and at best marginal beneficial effects. The benefits of PUFAs are much smaller than the effect sizes observed for traditional pharmacological treatments of ADHD. The effectiveness of PUFA supplements in reducing medication dosage has been suggested but needs to be confirmed. Zinc, iron, and magnesium supplementation may reduce ADHD symptoms in children with or at high risk of deficiencies in these minerals. However, convincing evidence in this regard is lacking.

Keywords ADHD · Nutritional supplements · Polyunsaturated fatty acids · Zinc · Iron · Magnesium

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common childhood-onset psychiatric disorder and may persist into adulthood. The disorder shows phenotypic heterogeneity and is characterized by impaired sustained attention, hyperactivity, and increased impulsivity and is associated with social, academic, vocational, and mental health problems. Approximately 3–5% of school children and adolescents are affected by ADHD; the prevalence has been shown to be higher in boys than girls [1–4]. The etiology of ADHD is

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✉ Klaus W. Lange
klaus.lange@ur.de

Joachim Hauser
joachim.hauser@ur.de

Katharina M. Lange
katharina_lange93@gmx.de

Ewelina Makulska-Gertruda
ewelina.makulska-gertruda@ur.de

Yukiko Nakamura
yukiko_nak@hotmail.com

Andreas Reissmann
andreas.reissmann@ur.de

Yuko Sakaue
taretare@belle.shiga-med.ac.jp

Tomoyuki Takano
tmyktkn@belle.shiga-med.ac.jp

Yoshihiro Takeuchi
takeuchi@belle.shiga-med.ac.jp

[1] Department of Experimental Psychology, University of Regensburg, Universitätsstrasse 31, 93040 Regensburg, Germany

[2] Department of Developmental and Behavioral Pediatrics, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Shiga 520-2192, Japan

[3] Department of Pediatrics, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Shiga 520-2192, Japan

multifactorial, i.e., social, environmental, neurobiological, and genetic factors have been suggested to be relevant [1, 5, 6].

The pathophysiology of ADHD remains elusive. The findings of various neurobiological investigations suggest that a dysfunction of dopaminergic and noradrenergic neurotransmission within frontostriatal brain regions is a neurobiological correlate of ADHD [7]. This hypothesis is supported by the fact that methylphenidate, the drug most commonly used in the pharmacological treatment of ADHD, increases the extracellular availability of these catecholamines by reuptake inhibition [8]. Atomoxetine is a relatively selective noradrenaline reuptake inhibitor [9] and is also in therapeutic use in individuals with ADHD [10]. For example, a decrease in activity of frontal cortical dopaminergic neurotransmission has been noted to be involved in the development of cognitive deficits, while subcortical dopaminergic overactivity may cause behavioral hyperactivity [6, 11–14]. Stimulant medications such as methylphenidate are frequently administered in individuals with ADHD, but they are not always effective. Concerns over adverse effects of pharmacotherapy have prompted research on alternative treatment strategies including the use of nutritional supplements. It has been shown that 12% of children with ADHD had used complementary or alternative medicines including dietary supplements [15]. The role of nutrition and nutritional supplements in the etiopathophysiology and treatment of ADHD has become a focus of clinical interest and research. ADHD has, for example, been associated with a Western-style diet high in fat and refined sugars and low in omega-3 polyunsaturated fatty acids (omega-3 PUFAs) and fiber [16]. Nutritional supplementation proposed for the treatment of ADHD mainly includes PUFAs and minerals [17, 18]. Many other natural supplements are used in the USA and other countries despite minimal or non-existent evidence of efficacy and possible side effects [18].

PUFA Supplements in ADHD

PUFAs play an important role in neuronal development and functioning of the central nervous system [19, 20]. Mammalian brains are rich in long-chain (LC) omega-3 and omega-6 PUFAs, particularly docosahexaenoic acid (DHA) and arachidonic acid (AA) [21, 22]. These PUFAs cannot be synthesized by mammals and need therefore to be provided by the diet (essential fatty acids (EFAs)). LC-PUFAs including AA, DHA, and eicosapentaenoic acid (EP) have been shown to influence various neuronal processes and to exert an effect on cognitive functions by modulating the neuronal membrane which can affect membrane receptors, neurotransmission, signal transduction, and neural plasticity [22, 23]. Changes in LC-PUFA concentrations in the neuronal membrane seem to lead to altered monoaminergic neurotransmission [24]. Studies in humans suggest that omega-3 fatty acid deficiency causes an imbalance of the omega-3/omega-6 PUFA ratio, thereby affecting neurocognitive abilities and inducing behavioral disorders including ADHD [20, 23, 25].

Several clinical observations led to the notion of a possible association between ADHD and EFAs. Children and adolescents with ADHD have been reported to show signs of fatty acid deficiency, such as dry hair and skin as well as polydipsia and polyuria, at least 30% more frequently than controls [25–29]. Several studies have shown a significant decrease in blood plasma levels of DHA, EPA, AA, and dihomogammalinolenic acid (DGLA) in children with ADHD compared to controls [25, 27, 30, 31]. A recent meta-analysis has examined whether ADHD is associated with alterations in blood lipid levels [32•]. This analysis included nine studies ($n = 586$) and found lower overall blood levels of omega-3 PUFAs in individuals with ADHD versus controls (95% CI = 0.26–0.59; $p < .001$) [32•]. This result suggests that omega-3 PUFA levels are reduced in children with ADHD and that nutritional PUFA supplements may be efficacious in the therapy of ADHD [33].

Numerous studies of varying scientific rigor assessing the efficacy of fatty acid supplementation in ADHD have been published over the last 20 years. In the following, the results of recent studies published since 2014 will be presented.

An omega-3 fatty acid mix (EPA/DHA) was assessed in a randomized, double-blind, placebo-controlled 16-week trial in 95 children with ADHD. The fatty acid supplementation increased EPA and DHA concentrations in erythrocyte membranes and improved working memory function, while no effects were observed in regard to other cognitive measures and the children's parent- and teacher-rated behavior [34].

A randomized, placebo-controlled, clinical trial assessed the effects of a 12-week supplementation of omega-3 and omega-6 fatty acids on biochemical and behavioral outcomes in 76 male adolescents aged 12–16 with ADHD [35]. In the LC-PUFA group, supplementation increased EPA, DHA, and total omega-3 fatty acid levels. However, no treatment effects were observed on the scores of the Conners' Teacher Rating Scales [35].

Another study assessed the effects of dietary omega-3 PUFA supplementation on ADHD symptoms in boys aged 8–14 years with ($n = 40$) and without ($n = 39$) ADHD [36]. In a 16-week double-blind randomized placebo-controlled trial, the boys consumed 10 g of margarine daily, enriched with either 650 mg of EPA/DHA each or placebo. The DHA level at follow-up was higher for boys receiving EPA/DHA supplements than for the placebo group [36]. EPA/DHA supplementation reduced symptoms of ADHD (parent-rated attention), both for boys with ADHD and typically developing boys [36].

In a randomized, double-blind 8-week clinical trial, the effect of zinc and omega-3 fatty acid supplements as adjunct treatment was assessed in 150 children aged 6–15 years and diagnosed as new cases of ADHD [37•]. In addition to the

standard treatment for ADHD (methylphenidate), the children received placebo in the control group ($n = 50$), omega-3 fatty acids ($n = 50$) in the second group, and zinc sulfate in the third group ($n = 50$). Clinical assessment was performed using Conners' Parent and Teacher Rating Scales at baseline and after 2, 4, and 8 weeks of treatment. In children with the attention-deficit disorder subtype of ADHD, the mean scores of the Conners' scale showed a significant improvement in the zinc group compared to those in controls [37•]. A better clinical response in the omega-3 group than in the other two groups indicated that omega-3 supplementation was superior to both zinc and placebo in the clinical improvement of ADHD [37•].

The omega-6/omega-3 PUFA ratio has been noted to be more important than the absolute levels of either. The omega-3 PUFAs EPA and DHA and the omega-6 PUFA AA were therefore analyzed in the erythrocytes of children with ADHD ($n = 401$) [38]. These participants showed reduced DHA, EPA, and AA levels and an increase in the omega-6/omega-3 and AA/EPA ratios compared to controls ($n = 79$) [38]. These parameters correlated significantly with ADHD symptoms. A recent meta-analysis has assessed the relationship between ADHD symptoms and blood omega-6/omega-3 or AA/EPA [39•]. In the five studies meeting the inclusion criteria, children and adolescents with ADHD had elevated ratios of both blood omega-6/omega-3 and AA/EPA fatty acids compared to controls. The pooled mean difference between individuals with ADHD and controls was 1.97 (0.90–3.04) for omega-6/omega-3 ($n = 5$ studies, I (2) 83%) and 8.25 (5.94–10.56) for AA/EPA ($n = 3$ studies, I (2) 0%) [39•]. An increase in omega-6/omega-3 ratio, and especially in regard to the AA/EPA ratio, may represent the underlying disturbance in EFA levels in ADHD [39•].

The evaluation of clinical trials aiming to assess the efficacy of nutritional PUFA supplements in ADHD is problematic due to various methodological problems. ADHD has not invariably been diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* [40], and various comorbid disorders were present in numerous individuals. The existing studies are heterogeneous in regard to both independent and dependent trial variables. For example, EFA precursors, omega-3 PUFAs, and omega-6 PUFAs or combinations of these compounds, different pharmaceutical forms, and various doses have been used. Furthermore, the assessment tools (e.g., behavioral/clinical observations, assessment scales, psychometric tests, neuropsychological evaluations) varied greatly among the available reports.

In addition to the above-mentioned clinical trials, several meta-analyses have recently been published in regard to PUFA supplementation in individuals with ADHD. Their main conclusions will be presented as follows.

A meta-analysis examined the efficacy of nutritional omega-3 PUFA supplements in children with ADHD and included 10 trials with a total of 699 children [41]. Omega-3 PUFA supplementation showed a small but significant effect in improving ADHD symptoms. However, the relative efficacy of omega-3 PUFA supplements was modest in comparison with the commonly used pharmacotherapies of ADHD [41].

Another meta-analysis included 13 trials with 1011 children and adolescents with ADHD and compared the efficacy of PUFAs to placebo or other forms of treatment in improving the symptoms of ADHD [42]. The majority of data indicated no benefit of PUFA supplementation, while some limited data showed an improvement following combined omega-3 and omega-6 PUFA administration [42].

A further meta-analysis included only randomized controlled trials regarding omega-3 and/or omega-6 supplements in ADHD ($n = 11$) [43]. When the best probably blinded assessment was employed, effects were significant for EFA supplementation (standardized mean difference = 0.16). The supplementation effects were significant and remained significant when the analysis was limited to nine trials with no or low medication [43]. However, it was noted that the effect size for PUFA supplementation was smaller than that of medications.

A larger sample of randomized supplementation trials than previously reported was included in a meta-analysis of the findings in regard to omega-3 PUFA administration in ADHD [32•]. The meta-analysis of 16 studies ($n = 1408$) showed that omega-3 supplementation improved ADHD composite symptoms [32•]. The supplementation showed reliable effects on hyperactivity by parent and teacher report, but reliable results for inattention by parent report only [32•]. Nutritional omega-3 PUFA supplements appeared to lead to modest improvements in ADHD symptoms.

Another recent review and meta-analysis of randomized controlled trials examined the effects of omega-3 PUFA supplements on cognition in healthy adults and typically developing children as well as in individuals with ADHD and related neurodevelopmental disorders [44•]. In the 24 included studies, omega-3 PUFAs did not improve any of the cognitive performance measures in the entire sample or the subgroups of typically developing children and ADHD and related disorders. Supplementation improved short-term memory in individuals with low omega-3 PUFA status [44•].

In order to assess which, if any, PUFA might be effective in improving ADHD symptoms, an updated meta-analysis of randomized clinical trials in ADHD was performed together with multivariable meta-regression analyzing data on PUFA content obtained from independent fatty acid methyl ester analyses of each study PUFA regimen [45•]. The overall pooled estimate from 18 studies demonstrated that combined ADHD symptoms rated by all raters were reduced following PUFA administration [45•]. However, when analyzed by rater, only parent-rated symptoms were significantly reduced. Multivariable meta-regression showed

that longer study duration, γ-linolenic acid (GLA), and the interaction between GLA and EPA were related to a marked reduction in inattention. PUFA regimen content was not associated with alterations in hyperactive-impulsive symptoms. This study provides modest evidence of PUFA efficacy, especially of GLA and EPA, in alleviating inattention symptoms in ADHD [45•].

Several randomized controlled trials have reported a beneficial effect of omega-3 PUFA supplementation on emotional lability and related behaviors which frequently co-occur with ADHD. A recent meta-analysis of 10 studies meeting the inclusion criteria assessed the effect of omega-3 PUFA supplementation on emotional lability and related domains (e.g., oppositional behavior, aggression, and conduct problems) in children with ADHD [46]. A primary analysis of omega-3 PUFA administration was unable to demonstrate improvements in regard to emotional lability, oppositional behavior, conduct problems, or aggression. Subgroup analyses of higher quality studies and those with strict inclusion criteria showed a marked decrease in emotional lability and oppositional behavior [46]. These results suggest small effects of omega-3 PUFA on reducing emotional lability and oppositional behavior in subgroups of ADHD children [46].

In the meta-analytical reviews, the number of studies included, the inclusion criteria, and the statistical models employed differed. It is important to note that some analyses included trials with non-ADHD participants. Given a high prevalence of co-occurring conditions in individuals with ADHD, clinical studies assessing the efficacy of PUFA supplements may have included participants both with and without comorbidities. The treatment response in patients with ADHD has been demonstrated to vary depending on the presence of comorbid conditions [47]. These factors may explain differences between the meta-analytical reviews which emphasizes the sensitivity of these analyses to variations in protocol. In some studies, PUFA supplementation may have been insufficient to influence brain PUFA levels due to low dosage and/or brief duration of PUFA administration. It also remains to be established if PUFA administration is effective at any time during the life span or if there is a critical age for positive effects to be seen as has been suggested by findings in a rat model of chronic omega-3 PUFA deficiency [48].

Mineral Supplements in ADHD

Minerals including zinc, iron, and magnesium have been proposed to play a role in the pathogenesis of ADHD, and supplementation of these minerals may therefore be beneficial in the treatment of this disorder [49, 50].

Zinc

Zinc homeostasis in the brain is closely related to neuronal activity, and zinc may serve as an endogenous neuromodulator in synaptic neurotransmission [51]. The findings of studies in humans and animals have suggested that zinc deficiency may be associated with hyperactivity and may also be involved in the pathophysiology of ADHD in children [52–54]. Blood serum levels of zinc have been demonstrated to be reduced in children with ADHD compared to healthy children [49]. The results of a meta-analysis suggest a significant association between low zinc levels and a diagnosis of ADHD [55].

A recent case-control study assessed the possible relationship between dietary/nutrient patterns and the risk of ADHD [56•]. This study included 592 Chinese children aged 6–14 years (296 with ADHD, 296 without ADHD); the matching variables were age and sex. Factor analysis and a food frequency questionnaire were used in order to identify dietary and nutrient patterns. A fish/white meat dietary pattern was shown to be inversely associated with ADHD. An inverse relationship could also be demonstrated for a mineral/protein nutrient pattern rich in zinc, protein, and other minerals [56•]. These dietary/nutrient patterns may therefore have beneficial effects on ADHD in Chinese children. In addition, blood zinc levels showed a negative association with ADHD [56•] and may be helpful in distinguishing ADHD.

In a large randomized clinical trial, 400 children with a primary DSM-IV diagnosis of ADHD (328 boys and 72 girls, mean age 9.6 years) were randomly assigned to a 12-week double-blind treatment with zinc sulfate (150 mg/day, $n = 202$) or placebo ($n = 198$) [57]. The children treated with zinc sulfate showed marked improvements in hyperactivity and impulsivity but not inattention, as assessed with the ADHD Scale, Conners' Teacher Questionnaire, and DuPaul Parent Ratings of ADHD.

In a 6-week randomized, double-blind, placebo-controlled trial, the effects of zinc sulfate (55 mg/day) plus methylphenidate (1 mg/kg/day) were assessed in 44 children with ADHD (26 boys and 18 girls, mean age 7.9 years) [58]. Add-on treatment with zinc sulfate resulted in a greater improvement in ADHD symptoms (Teacher and Parent ADHD Rating Scale) than the sole administration of methylphenidate.

Two other studies [59, 60] were unable to show any significant effects of zinc supplementation on ADHD symptoms. It is possible that insufficient doses of zinc produced results different from other studies.

A recent randomized, double-blind, 8-week clinical trial evaluated the effects of zinc and omega-3 fatty acid supplements as adjunct treatment in 150 ADHD children aged 6–15 years [37•] (see also above). In addition to the standard medication for ADHD (methylphenidate), the children received placebo in the control group ($n = 50$), zinc sulfate in

the second group ($n = 50$), and omega-3 fatty acids ($n = 50$) in the third group. Clinical assessment was performed using Conners' Parent and Teacher Rating Scales at baseline and in weeks 2, 4, and 8 of treatment. In children with the attention-deficit disorder subtype of ADHD, the mean scores of the Conners' scale showed a significant improvement in the zinc group compared to controls [37•]. These findings suggest that zinc supplementation as add-on to the main treatment significantly improves the symptoms of the attention-deficit disorder subtype of ADHD (for the results of omega-3 fatty acid supplementation, see above).

Randomized, placebo-controlled trials of zinc supplementation either as monotherapy or as an adjunct to psychostimulant administration have provided conflicting evidence of efficacy. This may be due to differences in the prevalence of zinc deficiency in the participants. Zinc supplementation may be useful in patients with an established or a high risk of zinc deficiency. However, an adequate dosage or form of supplementation cannot be recommended on the basis of the available findings.

Iron

Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme of monoamine synthesis and is therefore involved in the regulation of dopamine and noradrenaline synthesis [61]. Brain iron deficiency has been suggested to play a role in the pathophysiology of ADHD. Most studies on the iron status in individuals with ADHD measured serum ferritin, the major iron storage protein, as an index of peripheral iron status and reported inconsistent results [62]. In a meta-analysis of case-control studies, patients with ADHD have been demonstrated to have reduced serum ferritin concentrations compared to healthy controls [55]. In a recent study, 2805 children aged 10 years from two large population-based birth cohorts showed no indications of an association between peripheral ferritin levels and ADHD symptoms [63]. In a recent case-control study, the association between iron deficiency and ADHD was assessed in 630 children and adolescents with ADHD aged 5–18 years and 630 age- and sex-matched controls [64•]. Significant differences between ADHD and control participants were found for vitamin D, serum iron, ferritin, hemoglobin, and magnesium. Multivariate logistic regression analysis revealed that serum vitamin D, iron, ferritin, and calcium concentrations as well as physical activity were the main factors associated with ADHD after adjusting for age, gender, and other variables [64•]. These findings suggest that low serum iron and ferritin levels may be associated with ADHD.

A recent study compared iron deficiency parameters including serum iron, iron-binding capacity and serum ferritin in patients with stimulant-naive ADHD and healthy controls [65•]. Two hundred individuals with ADHD (100 ADHD-combine and 100 ADHD-predominantly inattentive) and 100 healthy participants were assessed. No significant differences in iron deficiency parameters were observed between ADHD patients and healthy controls [65•]. The same parameters were not significantly different between the ADHD presentations. The hyperactivity scores of the Conners' Rating Scale-Revised (Long Form Parent-Teacher) were negatively associated with the serum ferritin level in the ADHD group.

A significant comorbidity between ADHD and restless legs syndrome (RLS) has been proposed, and iron deficiency may underlie common pathophysiological mechanisms in individuals with ADHD plus RLS [66]. Studies investigating the role of brain iron and the efficacy of iron supplementation in ADHD need to address this issue.

Based on the preliminary findings of two cross-sectional studies, brain iron has recently been proposed to be a non-invasive biomarker of ADHD [67]. Children with ADHD have been reported to show significantly lower brain iron levels, estimated with magnetic resonance imaging (MRI), in both the right and left thalamus, compared to healthy controls [68]. It could also be shown that medication-naive patients with ADHD had significantly reduced MRI-based indices of brain iron in striatal and thalamic regions compared to either typically developing controls or psychostimulant-medicated individuals with ADHD [69]. The specificity of these observations remains to be established since estimated brain iron did not differ significantly between children with ADHD and psychiatric controls [68]. Further studies are required in order to prove the validity of brain iron as a biomarker of ADHD.

Magnesium

Magnesium is involved in the protection of neuronal cell membranes and the modulation of neurotransmitter release in the brain [70]. Magnesium is a cofactor for many enzymes and interacts with monoamine receptors supposedly involved in the pathophysiology of ADHD [71]. In case-control trials, serum levels of magnesium have been reported to be markedly reduced in children with ADHD compared with controls [49, 72, 73]. However, a relationship between reduced magnesium levels and ADHD was not supported by a meta-analysis of case-control studies [55].

An early investigation assessing the effect of magnesium supplementation (200 mg/day) over 6 months in hyperactive children with established magnesium deficiency in blood serum, erythrocytes, and hair demonstrated a significant decrease of hyperactivity compared to baseline evaluation and the control group [74]. Another study followed children with symptoms of ADHD during a magnesium-vitamin B_6 regimen (6 mg/kg/day magnesium, 0.6 mg/kg/day vitamin B_6) administered for at least 8 weeks [75]. The children with ADHD showed a significant decrease in intraerythrocyte

magnesium levels compared to controls. The combined administration of magnesium and vitamin B_6 for at least 2 months led to a significant increase in intraerythrocyte magnesium levels while the clinical symptoms improved, i.e., hyperactivity and hyperemotivity/aggressiveness were reduced, and school attention was improved [75]. When the administration of magnesium and vitamin B_6 was discontinued, the clinical ADHD symptoms reappeared within a few weeks and the intraerythrocyte magnesium values decreased [75].

In a recent study by El Baza et al. [76•], serum and hair levels of magnesium in 25 children with ADHD were compared to those in 25 healthy children. In addition, the effects of magnesium supplementation as an add-on treatment in magnesium-deficient children were assessed. A reduction in magnesium was found in 18 (72%) of children with ADHD. Magnesium-deficient patients were randomly assigned to two groups. One group received magnesium supplementation (200 mg/day) in addition to standard medical therapy. The other group received standard treatment alone. After 8 weeks, the groups were assessed using the Conners' Parent Rating Scale and the Wisconsin card sorting test. At follow-up examination, Conners' parent rating scale subitems improved in the group supplemented with magnesium, with a highly significant improvement in the hyperactivity and the impulsivity domains [76•]. Similarly, cognitive function at follow-up as assessed using the Wisconsin card sorting test showed significantly improved scores in the category completion and the conceptual level. Follow-up assessment of the ADHD group without magnesium supplementation showed no improvement of cognitive function and Conners' rating scale subitems. Twenty-two percent of patients receiving magnesium supplementation reported side effects such as mild diarrhea or abdominal pain. These findings suggest that magnesium supplementation for 8 weeks markedly reduced the clinical symptoms of ADHD.

The studies by Mousain-Bosc et al. [75] and Huss et al. [77] allow no conclusions as to the effects of the sole administration of magnesium supplementation in individuals with ADHD due to the combination of magnesium with vitamin B_6 [75] or PUFAs and zinc [77], respectively.

In summary, the notion that magnesium supplementation may be of benefit in ADHD is based on controlled cohort studies. So far, no randomized, placebo-controlled, blinded trials have demonstrated the efficacy of magnesium supplementation in the therapy of ADHD [78]. Major limitations of the available studies include the small number of cases and the short duration of supplementation.

Conclusion

The occurrence of ADHD has been associated with PUFAs, since individuals with ADHD have significantly reduced blood levels of PUFAs and, in particular, omega-3 PUFAs. Given the important role of LC-PUFAs in neuronal development and brain functioning, these observations suggest that nutritional PUFA supplements may improve the symptoms and problems related to ADHD. In addition, minerals such as zinc, iron, and magnesium have also been suggested to be involved in ADHD. Although (subgroups of) children with ADHD may show reduced levels of PUFAs, zinc, iron, and magnesium, a causative relationship between these changes and the occurrence of ADHD has not been proven.

There is marginal evidence that nutritional supplementation of omega-3 PUFAs or minerals (zinc, iron, magnesium) influences symptoms and/or cognition in individuals with ADHD. Pre-treatment PUFA and mineral status may influence the efficacy of nutritional supplementation of these compounds in ADHD, i.e., clinically relevant effects of supplements may be confined to individuals with respective deficiencies. Whether or not individuals with reduced PUFA and mineral status are more responsive to nutritional supplements remains to be assessed. Patient subgroups most likely to benefit from nutritional supplements as well as thresholds above which supplementation has little effect should be identified. Furthermore, minerals should be supplemented with caution, and overdosing must be avoided.

Both form and dosage of PUFA and mineral supplementation varied widely between published studies, and optimal dosage recommendations can therefore not be given.

If a critical time frame during development exists for an effective administration of omega-3 PUFAs [48], future research should assess if nutritional supplements in the early or even prenatal stages of the children's development may prevent the occurrence of ADHD. In addition, future investigations should employ larger samples and longer durations of supplementation. Future investigations need to address the limitations of available studies using nutritional supplements in the treatment of ADHD, i.e., they should employ well-defined participant selection criteria, larger trial samples, longer supplementation/follow-up durations and provide dose-response information.

Although the description of ADHD in international classification systems [40] seems to reflect a consensus regarding the clinical entity of ADHD, there is still considerable controversial debate about this issue [2, 79] since no distinctive etiology or pathophysiology has been identified and a remarkable overlap of ADHD symptoms exists with those of comorbid psychiatric disorders. Due to the phenotypic and etiopathophysiological heterogeneity of ADHD, potential therapeutic effects of nutritional supplements in ADHD might be confined to patient subgroups as yet not identified. Furthermore, the findings in clinically referred cases, i.e., narrowly diagnosed or severely affected individuals, may not allow the generalization to non-referred cases in the community.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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