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Dietary influences in Attention Deficit/Hyperactivity Disorder: an evidence-based narrative review

Mona Boaz*, Vered Kaufman-Shriqui

Director of Graduate Studies, Department of Nutrition Sciences, School of Health Sciences, Ariel University Ariel, Israel.

***Corresponding Author:** Mona Boaz, PhD, Professor, Director of Graduate Studies, Department of Nutrition Sciences, School of Health Sciences, Ariel University Ariel, Israel

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ABSTRACT

Background: A number of nutrients and dietary patterns have been proposed as therapeutic interventions for attention deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder prevalent in as many as 5% of school-aged children. Evidence for these claims is inconsistent.

Objectives: To estimate the efficacy of interventions with specific nutrients: vitamin D, omega-3 fatty acids, magnesium, iron, zinc, copper, and the Mediterranean diet pattern in reducing ADHD symptoms.

Methods: A narrative review of the literature

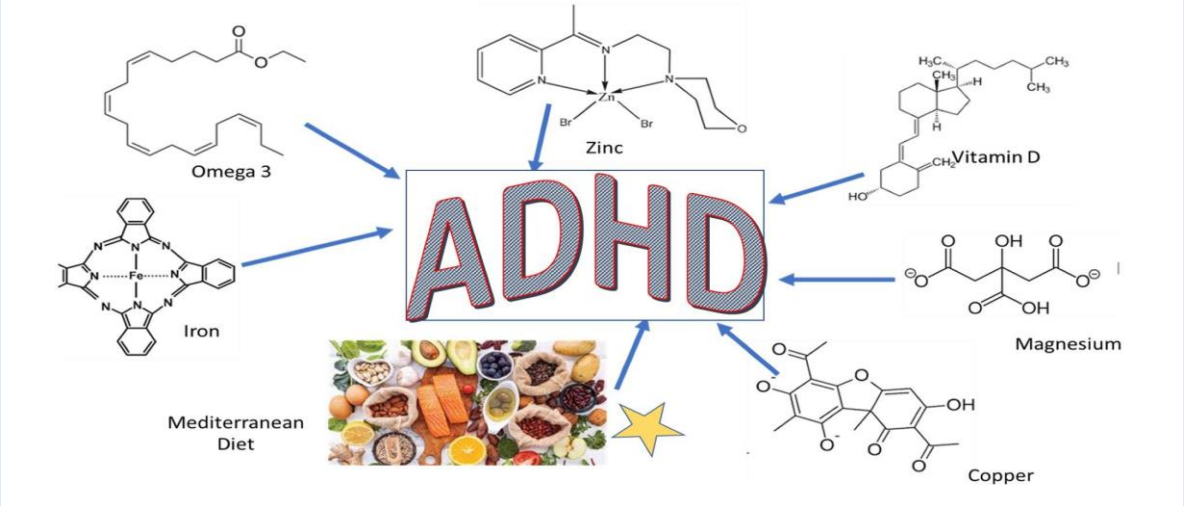
Results: The interventions considered herein have biological and physiological rationale supporting their proposed use in treating ADHD. Evidence supporting their use is frequently seen in observational studies, but this evidence is less convincing in clinical trials and meta-analyses.

Conclusions: Professional bodies do not recommend these interventions for the general ADHD population in the absence of documented deficiencies. Because the Mediterranean diet prevents chronic disease and promotes general health and wellness, it can be recommended as appropriate for children with ADHD.

Key words: Attention deficit/hyperactivity disorder (ADHD); vitamin D; omega-3 fatty acids; magnesium; iron; zinc; copper; Mediterranean diet

Graphic Abstract

While omega 3, zinc, vitamin D, iron, magnesium and copper all have a demonstrated biological mechanism underpinning their use as supplements in ADHD, only the Mediterranean Diet is recommended, but the recommendation is for general good health and disease prevention, not specific to children with ADHD



INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder with a global prevalence estimated of 5% in school-aged children [1]. Children with ADHD suffer from frequent comorbidities such as learning disabilities, behavioral problems, mental health, social difficulties, risk behaviors, and premature death in adulthood. The etiology of ADHD is multifactorial and merits a genetic basis. The contribution of nutrients and overall nutrition to the development or treatment of ADHD is mainly unknown, and studies have shown controversial findings [2].

Nutrition and specific nutrients have been studied as risk factors for ADHD, including food additives, food colorings, and added sugars [3]. This has led to using elimination diets to improve behaviors [4]. Elimination diets may omit specific foods/additives, such as food colorings or preservatives; or they may follow the Few Foods Diets, in which all but a few foods are removed from the diet and added back systematically to determine if changes in behavior can be detected [4]. These diets have been shown to produce inconsistent results, and studies in which improvements are detected are parent-reported; by contrast, behavior ratings from non-parent raters did not show significant improvement following elimination diets [5].

In addition to removing foods from the diet, specific nutrients have been examined as potential ADHD interventions, primarily for their antioxidant and/or immunomodulatory characteristics [6-7]. Among them are vitamin D, Omega 3, and the minerals magnesium

iron, zinc, and copper. The Mediterranean diet pattern has also been examined as a potential dietary intervention for children with ADHD.

METHODS

This narrative review, which included queries to PubMed, EMBASE, Cochrane and UpToDate; the search words, “attention deficit and hyperactivity disorder” were used together with “nutrients," or "diet” or “supplements,” or “intervention,” or “treatment.” This led to the identification of nutrients (vitamin D and omega 3) and minerals (magnesium, iron, zinc, and copper). Searches progressed by entering "ADHD" and each one of the identified nutrients. Further, the search "ADHD" and "Mediterranean Diet" was entered into each of the databases. While the original search was limited to the last five years, some older papers were included to reference possible mechanisms of action.

Nutrients suspected as associated with ADHD

Vitamin D: Among pregnant women whose children were later diagnosed with ADHD, serum 25(OH) D (vitamin D) levels were significantly lower during the first trimester of pregnancy than among women whose children did not subsequently develop ADHD [8]. Serum vitamin D levels have also been shown to be significantly lower in children with vs. without ADHD [9].

Vitamin D synthesizes of dopamine, acetylcholine, and norepinephrine, neurotransmitters associated with ADHD symptoms, including inattention, impulsivity, and hyperactivity [10]. In an interventional study, serum vitamin D levels were measured in children aged 7-14 years with ADHD. These children were categorized as vitamin D deficient or adequate. Children with a deficiency were allocated to receive supplemental vitamin D, while those without a deficiency received a placebo. Children in the vitamin D supplement group exhibited significant improvements in conceptual level, inattention, hyperactivity, opposition, and impulsivity at 12 weeks of follow-up compared to the placebo group, [11]. While the authors concluded that vitamin D supplementation in children with ADHD improved cognitive function and symptoms, it cannot be overlooked that the supplemented group had significantly lower serum vitamin D levels at baseline. Among children with ADHD aged 6-13 significant improvement in some behavioral measures in children randomized to 1000 IU vitamin D3 vs. placebo participating in an RCT of vitamin D supplementation [12].The Committee on Nutrition, the German Society for Pediatric Endocrinology, and the German Society for Pediatric and Adolescent Medicine Diabetology jointly recommended vitamin D supplementation in children older than two years, noting that this intervention has no impact on hyperactivity/attention deficit [13]. By contrast, a meta-analysis of vitamin D supplementation for ADHD found that vitamin D supplementation in methylphenidate-treated children with ADHD was associated with minor improvements in inattention, hyperactivity, and behavior scores (but not oppositional scores). However, the quality of the included studies was low overall, underlining the importance of high quality randomized clinical trials to evaluate the efficacy of this intervention definitively [14].

The rationale and recommendations for the use of Vitamin D supplements in children with ADHD are shown in Table 1.

Omega 3 Fatty Acids: Omega 3 fatty acids are derived from diet-obtained alpha-linolenic acid, acted upon by hepatic desaturases to generate eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [15]. Among the metabolic products of EPA are prostaglandins, thromboxanes, leukotrienes, and resolvins. DHA also generates resolvins as well as neuroprotectin D1 and other molecules leading to an overall anti-inflammatory

metabolic milieu [16]. Both EPA and DHA are integrated into cell membrane phospholipids, including in the central nervous system, where DHA levels are exceptionally high. Maintenance of omega-3 phospholipid levels appears to be associated with adult dietary intake [17]. Further, omega-3 fatty acids have been shown to have neuroprotective properties, modulating cell signaling and receptor transduction [18].

Table 1: Summary of Nutrients and Diets, the Rationale for their Use in ADHD and Evidence/Recommendations

Nutrient/Diet	Rationale	Evidence/Recommendations
Vitamin D	Neurotransmitter synthesis; ADHD symptoms	Supplementation recommended for all children, not specifically for ADHD; some RCT support
Omega-3 fatty acids	Anti-inflammatory properties; ADHD symptoms	Not supported by RCTs, meta-analyses; not recommended for ADHD
Magnesium	Neurotransmitter synthesis; ADHD symptoms	RCTs lacking; no recommendation for ADHD
Iron	Neurotransmitter synthesis; cognitive symptoms	Some RCT evidence; no recommendation for ADHD
Zinc	NDMA, GABA synthesis; ADHD symptoms	RCT, meta-analysis support; recommended for children with zinc-treatable comorbidities
Copper	Catecholamine synthesis; ADHD symptoms	Some RCT support; no recommendation for ADHD
Mediterranean Diet	Chronic disease prevention; ADHD symptoms	Recommended in general, not specifically for ADHD

Serotonin, the primary neurotransmitter, is associated with many behaviors dysregulated in ADHD, including executive function and impulsivity. It has been proposed that EPA increases neuronal serotonin release, and DHA controls serotonin receptor function. Thus, inappropriate intake of omega 3s during development might represent a mechanism through which ADHD develops [19]. This suggests that omega-3 supplementation might improve ADHD symptoms.

Consistent with this prediction, a small pilot study found that eight weeks of supplementation with 16.2g EPA/DHA concentrates/day resulted in improved inattention, oppositional behavior, hyperactivity, and conduct disorders in children [20]. A meta-analysis confirmed these findings and noted that EPA or DHA supplementation improved inattention, clinical symptom scores, and performance measures [21]. By contrast, a meta-analysis of omega-3 supplementation in children with ADHD using data for more than 1700 children, found no evidence of efficacy, including parent-rated or teacher-rated symptoms, behavioral difficulties, or quality of life. The authors concluded that while adverse events were not increased in supplemented children, the evidence of efficacy was lacking and precluded the recommendation of this intervention [22].

The rationale and recommendations for the use of omega-3 supplements in children with ADHD are shown in Table 1.

MINERALS: MAGNESIUM, IRON, ZINC, AND COPPER

Magnesium: Integral in the synthesis of omega-3 fatty acids, magnesium is a cofactor in desaturases and thus may participate in the regulation of ADHD symptoms [23]. Magnesium deficiency has been associated with inattention and aggression, common ADHD behaviors [24]. A meta-analysis identified significantly lower serum magnesium levels in children with ADHD vs. controls [25]; however, serum magnesium levels are not consistently reported as more deficient in children with ADHD. One study reported lower hair magnesium and greater urinary magnesium excretion in children with ADHD but no significant differences in serum magnesium [26]. A quasi-experimental study indicated magnesium supplementation was associated with improved magnesium nutriture and a reduction in hyperactivity [27]. However, these findings have not been replicated. Recent clinical guidelines for using nutraceuticals in treating ADHD did not include magnesium recommendations [28].

The rationale and recommendations for the use of magnesium supplements in children with ADHD are shown in Table 1.

Iron: Iron is a cofactor of tyrosine hydroxylase, a critical step in dopamine norepinephrine synthesis [29]. Iron deficiency can lead to disturbances of cognitive function and has been shown to be a common comorbidity in children with ADHD [30]. This forms the basis upon which iron has been hypothesized to influence ADHD symptoms. In a small study of iron supplementation in children with iron deficiency and ADHD, adding 80mg/day of ferrous sulfate did not significantly improve parent- or teacher-rated ADHD symptom scores compared to the placebo group [31]. Another study examined the role of iron supplementation (5 mg/kg/day) vs. placebo in children with methylphenidate-treated ADHD. After two months of follow-up, inattentiveness and hyperactivity scores were significantly lower in the supplemented group, though these scores had also improved in the placebo group [32]. It is noteworthy that iron supplementation was not included in the recommendations for the nutraceutical treatment of ADHD [28]."

The rationale and recommendations for the use of iron supplements in children with ADHD are shown in Table 1.

Zinc: Zinc is involved in the metabolism of neurotransmitters including N-methyl-D-aspartate (NMDA) [33], and gamma-aminobutyric acid (GABA) [34], both of which have been implicated in the pathogenesis of ADHD [35]. Zinc deficiency symptoms may include inattention, hyperactivity, and cognitive developmental delays like those observed in ADHD [36]. Children with ADHD were shown to have lower serum zinc levels less than controls [37], but zinc levels in blood or hair did not differ between children with ADHD and controls in a meta-analysis [38]. Several small clinical trials have indicated that zinc supplementation confers a treatment benefit for ADHD symptoms. For example, a study of 44 children with methylphenidate-treated ADHD was allocated 55 mg/day of zinc sulfate or a placebo. After six weeks, both parent- and teacher-rated scales improved in the zinc-supplemented group vs. controls [39]. A meta-analysis detected a slight improvement in total ADHD scores but failed to find a significant improvement in hyperactivity or inattention scores in school-aged children with ADHD supplemented with zinc vs. placebo [40]. Clinical guidelines note that zinc supplementation may benefit in children with ADHD and comorbidities leading to immune dysfunction, chronic inflammation, or oxidative stress and has acceptable tolerability in adults if the dose is less than 40 mg/day [28].

The rationale and recommendations for the use of zinc supplements in children with ADHD are shown in Table 1.

Copper: Copper is essential to the function of noradrenergic neurons, where it converts dopamine to norepinephrine through dopamine-β-hydroxylase and promotes catecholamine balance [41]. Despite this, associations between blood copper levels and parent- or teacher-rated ADHD scores have not been observed in children, and differences in blood copper levels between children with vs. without ADHD have not been detected [42]. Hair levels of copper (as well as zinc and magnesium) were lower in children with ADHD than in controls [43]. Consistent with this, dietary copper intake was shown to be lower in children with ADHD than in controls [44]. Nevertheless, copper is not mentioned in the guidelines for the nutraceutical treatment of ADHD [28].

The rationale and recommendations for the use of copper supplements in children with ADHD are shown in Table 1.

Mediterranean Diet Pattern: The Mediterranean diet is characterized by a low intake of saturated fats and added sugars and a high intake of olive oil, vegetables, fruits, cereals, nuts and pulses/legumes, moderate intake of fish, poultry, and other lean meat, moderate intake of dairy products and red wine [45]. This diet pattern is high in vitamin D, omega 3 fatty acids, and minerals while being low in sugar and food additives [46]. This pattern represents a step away from the processed food consumption typical of Western diets and is associated with a lower risk for certain cancers, cardiovascular disease, and dementia [47]. In contrast to a more reductionist approach in which individual nutrients are considered for intervention to prevent/treat ADHD, the Mediterranean diet can be conceived of as a more holistic approach. A number of studies have suggested a protective role of the Mediterranean diet in ADHD. For example, a cross-sectional study conducted on 41 children with ADHD and 48 controls found that consuming a Mediterranean diet significantly reduced the odds of ADHD [48]. Consistent with these findings, a case-control study in 120 children with ADHD and 240 matched controls identified a relative reduction in odds for ADHD of 51% for each tertile increase in adherence to the Mediterranean diet [49]. Nevertheless, these findings were not identified in a randomized clinical trial in which 60 children aged 6-16 years with ADHD were randomized to one of four groups: Mediterranean diet; supplementation with omega-3 fatty acids; Mediterranean diet plus supplementation with omega-3 fatty acids (137.5 mg EPA and 56.25 mg DHA in each of four flavored gel caps consumed daily); or control. After eight weeks of intervention, impulsivity scores declined only in the group assigned to supplementation with omega-3 fatty acids. Impulsivity decline was not observed in children assigned to the Mediterranean diet intervention nor in the group assigned to the Mediterranean diet with omega-3 fatty acid supplementation [50]. In conclusion, those findings do not support the role of the Mediterranean diet in treating symptoms of ADHD.

The rationale and recommendations for the use of the Mediterranean diet in children with ADHD are shown in Table 1.

CONCLUSION

The interventions considered herein - vitamin D, omega 3 fatty acids, magnesium, iron, zinc, copper, and the Mediterranean diet - have sound biological logic underpinning their consideration for treating ADHD. Many of these interventions have evidence supporting them in observational studies, but results have become less convincing in clinical trials and meta-analyses.

Professional bodies do not broadly make recommendations for these interventions.

Recommendations for these interventions are not broadly made by professional bodies; on the other hand, prohibitions are also not issued since most are well-tolerated. Because supplementation is less physiologic than dietary patterns, and because much evidence supports the consumption of the Mediterranean diet pattern for chronic disease prevention, it seems that recommending this pattern to children with ADHD is prudent. Even if no direct benefit to ADHD symptoms can be attributed to this diet, the Mediterranean pattern can support overall health and wellness in this population.

Abbreviations: ADHD: attention deficit hyperactivity disorder**,** EPA: eicosapentaenoic acid**,** DHA: docosahexaenoic acid**,** NMDA: N-methyl-D-aspartate**,** GABA: gamma-aminobutyric acid

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Competing Interests: Both authors declare that there are not conflicts of interest.

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