ALINEA

NUTRITION

APRIL 2022

www.alineanutrition.com

TABLE OF

CONTENTS

Lundbergh B, Enevoldsen AS, Stark KD, Ritz C, Lauritzen L. Fish oil supplementation may improve attention, working memory and attention-deficit/hyperactivity disorder symptoms in adults with autism spectrum disorder: a randomised crossover trial. *British Journal of Nutrition*. 2022;1–11.

What We Know, Think We Know, or Are Starting to Know

We know that the long-chain omega-3 fatty acids, EPA and DHA, play vital neurological roles [1]. EPA and DHA regulate and lower brain inflammation, increase brain cell membrane fluidity, and preserve synaptic function [1,2]. In otherwise healthy adults, omega-3 fatty acid supplementation has also been shown to improve cognitive testing, in particular attentional and complex processing tasks [3].

Ok, so that may be otherwise healthy adults. What of Autism Spectrum Disorder [ASD]? Long have I hummed and hawed about delving into this area of nutrition research. It' s complex, messy, while also being an emotive topic.

But we' re taking the plunge, because there is a plethora of nutritional abnormalities that have identified in children with ASD* [4]. Our focus in this Deepdive is omega-3 fatty acids. In children with ASD, an imbalance of fatty acids in membrane phospholipids has been shown, characterised by decreased EPA and DHA levels, and an imbalanced ratio of EPA to arachidonic acid [AA] [5]. Children with ASD have been shown to have 20% lower levels of total omega-3's, 23% lower DHA specifically, and 18% lower AA, compared to non-ASD controls [6].

As you can see, much of the research to date has focused on paediatric populations. Given these potential abnormalities in essential fatty acid metabolism, however, what would be the effect of omega-3 supplementation in adults with ASD? The present study investigated this question.

*Geek Box: Nutritional Abnormalities in ASD

The caveat before we outline some of the nutritional characteristics of ASD is that, as stated above, most of the evidence is derived from children. Nevertheless, these analyses have provided some fascinating insights into the nutritional abnormalities associated with ASD. First off, what do we mean by 'abnormalities'? We are referring to a normal distribution, i.e., the statistical concept represented by a bell-curve with the mean [i.e., the average] in the middle, and the percentages of a population covered by standard deviations[SD] from the mean: one SD [68.72%], two SD [95.45%], and three SD [99.73%]. Children with ASD are defined by abnormally distributed nutrient intakes; while for most micronutrients children with ASD will exhibit levels within the 10th to 90th percentile, up to 25% lie below or above these reference ranges, depending on the nutrient. For example, abnormally uneven distribution of vitamin B6, from subsets ranging high in red blood cell B6 levels to subsets with pronounced B6 deficiency. Such abnormal distributions are observed across several nutrients, indicative of the multifaceted presentations and different phenotypes in ASD. Some interesting nutrient characteristics have been observed. For example, low lithium levels in children with ASD have been characterised, and lithium is required as a co-factor in the function of two enzymes linked to ASD symptoms. Another observed abnormal nutritional characteristic is elevated copper-to-zinc ratio, which has been associated with behavioural disorders. Biotin has also been shown to be lower in children with ASD compared to non-ASD controls, and biotin is required as a co-factor in fatty acid synthesis, while deficiencies in biotin in experimental models result in neurological deficits. Certain underlying metabolic dysfunctions have been identified, which may also relate to ASD symptoms and behavioural disorders, including elevated oxidative stress levels and damage to cell membrane phospholipid layers. The latter appears to be associated with fatty acid metabolism abnormalities, which may be relevant for omega-3 status and related central nervous system disorders. A very important point to bear in mind is that whether these nutritional correlates of ASD are a consequence or cause of the condition is unknown.

The Study

The study was designed as a randomised, double-blind, controlled and crossover trial in adults with a self-reported diagnosis of ASD. The intervention tested the effects of a fish oil [FO] supplement compared to a safflower oil [SO] supplement, each taken for 4-weeks by the participants.

- FO: 5.2g total omega-3' s [2.4g EPA and 1.6g DHA] per day
- SO: 2.8g omega-6 linoleic acid per day

Participants were instructed to take four capsules, twice per day, for the 4-week period. Participants were tested before and after each phase of the intervention. The primary outcome was short-term spatial working memory and test of attention; secondary outcomes included a colour and word test in addition to other tests of ADHD symptom scores.

As Attention-Deficit-Hyperactivity Disorder [ADHD] is a common comorbidity with ASD, the researchers hypothesised that any effect of FO would be more pronounced in participants with combined ASD+ADHD.

Results: 22 participants completed the trial, with an average age of 28, of which there was a 50:50 male-female split. Fatty fish was reportedly consumed an average of 3.1 portions per month. Within the diagnoses of ASD, 19 participants reported Asperger' s Syndrome, while ADHD was also reported in 14 participants and depression in 13.

- ***Primary Outcomes*:** The visuo-spatial working memory score increased by 12 points [95% CI 1 to 23 points] following the FO phase compared to the SO phase. In relation to the test of attention, the percentage of total errors decreased by 0.7% [95% CI 0.6 to 1.0%] following the FO phase compared to the SO phase.

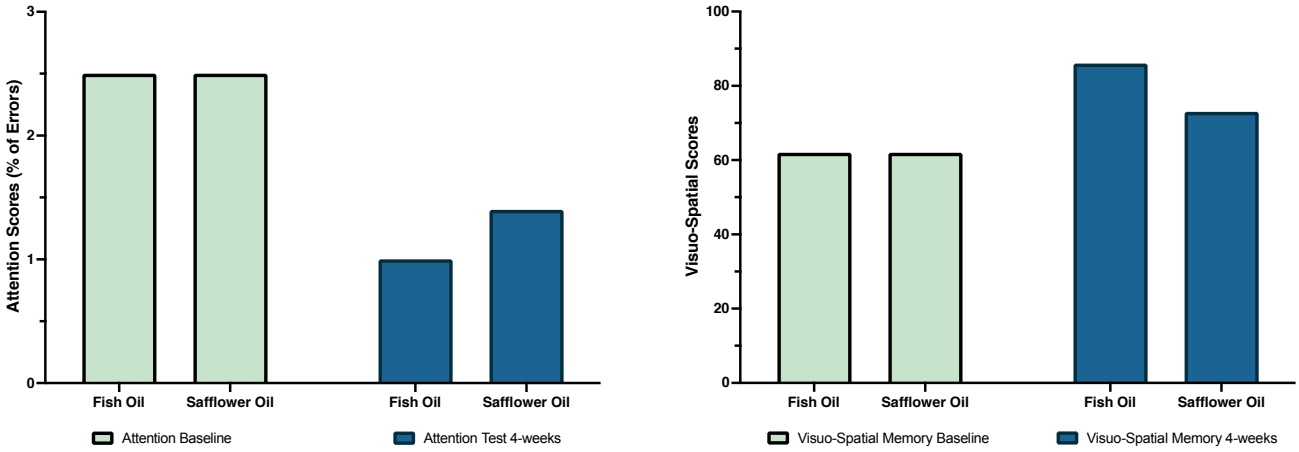

__Figure__ illustrating the differences in the primary outcomes with [__left__] attention scores from baseline to after 4-weeks of the fish oil and safflower oil supplementation, and [__right__] visuo-spatial scores from baseline to 4-weeks. The fact that there was an improvement in the SO group suggests a habituation effect of the cognitive tests, which is a common methodological issue for any studies on cognitive function, i.e., participants get better at the specifics of the test from baseline having already taken the test. Nevertheless, it is clear that participants overall performed better on these tests following FO supplementation.

- ***Secondary Outcomes*:** Cognitive flexibility, assessed by response times, improved following FO supplementation by 1.6 seconds [95% CI 0.6 to 2.6 seconds]. In relation to total ADHD symptoms, scores decreased by 2.0 [95% CI 0.3 to 3.7] following FO supplementation compared to the SO phase. This change was primarily driven by an improvement in inattention scores of 1.6 points [95% CI 0.5 to 2.7 points] following FO supplementation [more under ***Interesting Finding***, below].

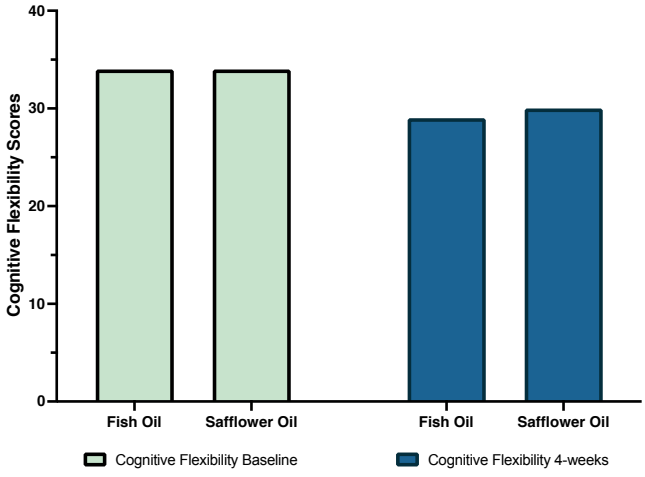

__Figure__ illustrating the differences in cognitive flexibility scores from baseline to after 4-weeks of the fish oil and safflower oil supplementation. This test shows a word card, a colour card, and a word-colour card. Participants must identify the word and colour, however, the challenge comes with the word-colour card: for example, this is where the word 'Blue' appears on the screen but the word itself is coloured in red. The correct answer is 'Red' – the colour of the letters – not the word itself. The score reflects the time to respond with the correct answer.

The Critical Breakdown

Pros: The trial was preregistered, and had a strong design as a randomised, crossover [so each subject served as their own 'control', i.e., each participant completed both phases and so the average effect in each phase is not influenced by inter-individual differences] study. The method of randomisation was appropriate [random number generator], and participants were randomised to the order of diet [e.g., FO>SO vs. SO>FO], which would account for potential effects of diet order. The primary and secondary outcomes were clearly stated. Compliance was verified both with self-reporting, counting of returned capsules, and blood measures of fatty acids, and each correlated showing high adherence.

Cons: Although the study attempted double-blinding, this was not achieved. This may have been because the capsules for the FO and SO differed in both smell and taste, and the authors report that 77% of participants correctly guessed the allocated sequence of oils [i.e., whether they were getting FO or SO first], and 68% of the investigators guessed correctly. 8 pills per day also seems like a substantial pill burden if we are thinking about wider generalisability of the intervention. There was no power calculation [i.e., the sample size estimate], so it is possible that this small study lacked power to detect differences from the intervention, and the reported effect sizes are small. Background fatty fish intake does not appear to have been controlled for, so it is possible that if fatty fish was being consumed during each phase, this would have provided less of a true comparison of the effects of FO.

Key Characteristic

The key characteristic of this study is the fact that it was conducted in adults. As stated above, the overwhelming majority of research into nutrition and ASD has focused on paediatric populations. There is a lack of research into adults, and this has left many open questions, in particular whether some of the benefits for dietary interventions in children may also be observed in adults. A previous trial in 19 adults with severe ASD found no effect of omega-3 supplementation, but the dose used was 0.93g per day of *combined* EPA and DHA [(7)]. This may be too low to observe any beneficial effect, particularly in the context of potential underlying metabolic dysfunction in polyunsaturated fatty acids in nervous system cell membranes [more under ***Relevance***, below]. Thus, while itself limited, the present study begins to fill what remains a big gap in the nutrition research on ASD.

Interesting Finding

In the main analysis which did not distinguish between participants with or without ADHD, there was no significant difference observed in relation to hyperactivity scores. However, in the sensitivity analysis which stratified participants according to whether they had ADHD or not, there was a significant improvement observed in relation to hyperactivity in those participants with ASD *and* ADHD. This is interesting because improvements in hyperactivity have been reported in the paediatric ASD research on omega-3 supplementation, however, this body of evidence is small and not always methodologically sound [8].

However, this may not be confined to ADHD in the context of autism. A recent meta-analysis of the effects of omega-3 supplementation in children with ADHD alone [i.e., non-ASD] found significant improvements in clinical ADHD scores, and hyperactivity and attention scores [9]. Thus, omega-3 supplementation appears to benefit ADHD independent of ASD. The fact that the present study, in an adult population, shows improvements in ADHD symptoms and specific subcomponents – such as hyperactivity – in the context of ASD is encouraging for the potential application of omega-3 supplementation in this population group.

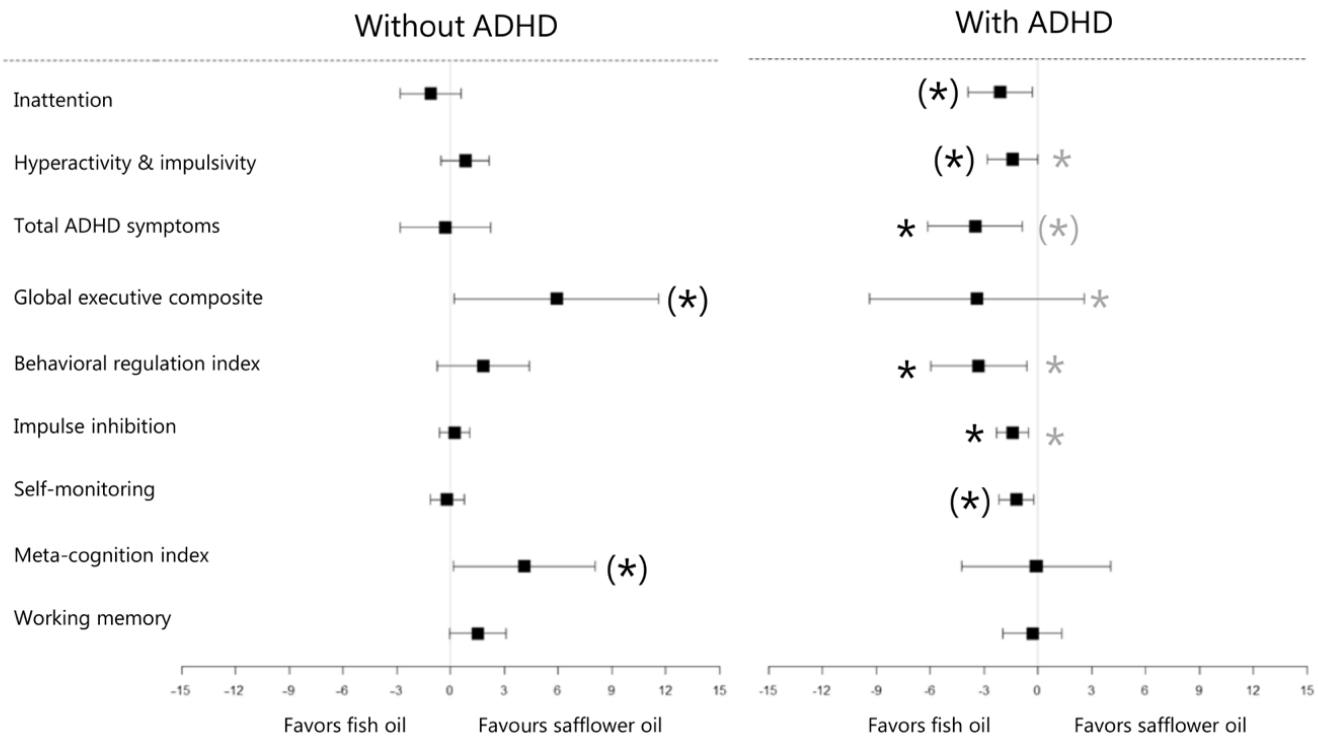

Figure *illustrating the differences in outcomes stratifying participants with ASD according to their ADHD status. The asterix represent measures that were significantly different between ADHD status. Of particular interest are the improvements in inattention, hyperactivity, and behavioural outcomes in those with ADHD, effects which were not observed in participants without ADHD.*

Relevance

The present study is best thought of as hypothesis-generating in relation to cognitive and behavioural improvements in adults with ASD, given that the sole prior trial in this area found no effects. There are clear differences in the interventions deployed in that previous trial and the present study, with a dose of barely 1g/d used in the former while the present study used 5.2g/d total.

Why might higher doses be crucial? There appears to be some profound underlying metabolic dysfunction in long-chain polyunsaturated fat [PUFA] metabolism in cell membranes. One study analysed levels of long-chain omega-3 fatty acids in red blood cell samples from a patient with ASD, based on whether they were stored in –20-degrees Celsius or –80C [5]. What they found was that if samples were stored at –20C, there was a loss of membrane long-chain PUFA of 70%. This was followed up by a study which showed a loss in red blood cell membrane long-chain PUFA of 60–82% following 6 weeks storage at −20°C, compared to healthy control samples [10].

You might be thinking what the relevance of the cold storage is; freezing would be expected to stabilise the fatty acid composition of the blood samples. The fact that it does not suggests that *in vivo* [i.e., in live humans], long-chain omega-3 fatty acids are highly unstable. Remember that these fatty acids, including AA, comprise up to half of all fatty acids present in nervous system cells. The hypothesis that excessive loss of these fatty acids from nervous system cells contributes to nervous system and behavioural disorders extends beyond autism, to conditions like schizophrenia and ADHD.

But despite these potential underlying metabolic factors related to essential fatty acid metabolism, currently the evidence-base remains woefully underfunded, underpowered, and underwhelming.

Application to Practice

In one of the most pragmatic papers you could read about nutrition generally, but in fact was specific to ASD, specialist dietitian David Rex wrote the following [11]:

"Unfortunately, there are very few well designed trials on diet and ASD or ADHD…Commercial and practical constraints mean there are substantial barriers to nutrition research per se, with drugs trials being easier to fund and design than nutrient trials, and nutrient ones being easier than those involving real foods or whole diets. If we based our public health nutrition policy only on the analysis of blinded, placebo controlled trials, what would we be recommending as the cornerstones of a healthy diet?"

For ASD, this is complicated by the fact that there is a common theme in the research: that *some* people with ASD benefit from a given intervention. This reflects the different phenotype presentations of ASD, and with such inter-individual differences it becomes almost impossible to make general recommendations. The challenge for nutrition, to quote Rex again, is that people will make decisions to consume certain foods or supplements with conditions like ASD *"whether the 'evidence base' is complete or not."*

In relation to the latter, Bent *et al.* [8] highlighted a high prevalence of use of omega-3 supplementation in ASD, while also indicating their safety profile. Yet, we don' t have the quality of evidence to specifically recommend their use. For nutrition professionals who may find themselves in this type of tricky situation, i.e., parents or carers are going to try one way or the other, what to do? The pragmatic approach would be to determine the benefits of supplementation using outcome-based decisions on behavioural effects with parental/carer input under supervision of a qualified nutrition professional.

References

1. Dyall SC. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. Frontiers in Aging Neuroscience. 2015;21;7.
2. Bradbury J. Docosahexaenoic acid (DHA): An ancient nutrient for the modern human brain. Nutrients. 2011;3(5):529–54.
3. Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. European Journal of Clinical Investigation. 2005;35(11):691–9.
4. Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. Nutrition & Metabolism. 2011;8(1):34.
5. Bell JG, Sargent JR, Tocher DR, Dick JR. Red blood cell fatty acid compositions in a patient with autistic spectrum disorder: a characteristic abnormality in neurodevelopmental disorders? Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA). 2000;63(1–2):21–5.
6. Vancassel S, Durand G, Barthélémy C, Lejeune B, Martineau J, Guilloteau D, et al. Plasma fatty acid levels in autistic children. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA). 2001;65(1):1–7.
7. Politi P, Cena H, Comelli M, Marrone G, Allegri C, Emanuele E, et al. Behavioral Effects of Omega-3 Fatty Acid Supplementation in Young Adults with Severe Autism: An Open Label Study. Archives of Medical Research. 2008;39(7):682–5.
8. Bent S, Bertoglio K, Hendren RL. Omega-3 Fatty Acids for Autistic Spectrum Disorder: A Systematic Review. Journal of Autism and Developmental Disorders. 2009;39(8):1145–54.
9. Chang JPC, Su KP, Mondelli V, Pariante CM. Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: a Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. Neuropsychopharmacology. 2018;43(3):534–45.
10. Bell JG, MacKinlay EE, Dick JR, MacDonald DJ, Boyle RM, Glen ACA. Essential fatty acids and phospholipase A2 in autistic spectrum disorders. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2004;71(4):201–4.
11. Rex D. An Evidence-based, “Common Sense” Approach to the Evaluation of Dietary Interventions in ASD and ADHD. Food and Behaviour Research. 2010;1–6.