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Role of Omega-3 Fatty Acids and Autism Spectrum Disorder: A Systematic Review

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Abstract

This systematic review examines the relationship between omega-3 supplementation and autism spectrum disorders (ASD). A comprehensive literature search was conducted across multiple databases, including PubMed, Cochrane Library, Web of Science, EMBASE, and relevant articles published since 2010. Following systematic screening, 10 clinical controlled studies met inclusion criteria. The review assessed intervention effects on ASD core symptoms, including social interaction, behavioral functioning and speech function. The findings indicate that omega-3 supplementation alone has minimal impact on alleviating ASD core symptoms.

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Introduction

The neurological illness known as autism spectrum disorder (ASD) is typified by repetitive behaviors, communication difficulties, and deficiencies in social interaction with the onset before the age of three years (1) . ASD is a heterogenous condition with increasing prevalence globally, is impacting almost one out of every 100 children globally. ASD diagnoses are three to four times as common in men than in women (2).

Socially inappropriate behavior is common among people with ASD, and they often struggle to comprehend how others behave in social situations (3).

They might struggle with social reciprocity, identifying and expressing particular emotions, and gauging other people's moods. As a result, they are commonly perceived as distant and disconnected. Along with language problems (such as pragmatic and semantic deficits), people with ASD frequently exhibit atypical eye contact patterns (such as prolonged eye contact) (4).

Some people with ASD may exhibit self-harming behaviors, such as head-banging, which is frequently linked to the more severe autism spectrum disorders, and motor stereotypical behaviors, such as hand flapping, rocking, and body spinning (5). People with ASD find new experiences extremely challenging. Toys are often used in restricted and unusual ways by children with ASD, such as spinning or flapping things for prolonged periods. Along with avoiding social connection and preferring solitary play, they also struggle with imaginative symbolic play that involves pretense (6). Children with ASD find it challenging to play and form strong bonds with other kids when they struggle with social contact, and they are also more likely to be bullied (7).

Polyunsaturated fatty acids known as essential fatty acids are produced by the body but are required for the brain and immune system to develop and operate normally (8). Essential fatty acids are classified into several major categories. Fish and seafood are rich sources of long-chain omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (5). Short chain omega-3 fatty acids called alpha-linolenic acids (ALA) are found in soya beans, cereals, and flaxseed. Attention deficient/hyperactivity disorder, dyslexia, and dyspraxia are among the

neurodevelopmental disorders that have been associated with omega-3 deficits or imbalances in the omega-3:omega-6 ratio (9).

Any potential therapeutic advantage of omega-3 is predicated on the idea that the current diet either has an excess of omega-6 fats in comparison to omega-3 fats or is lacking in omega-3 fats (a condition known as "fatty acid imbalance" (10). Increased intake of foods treated to remove omega-3 fats, frequently through hydrogenation, to extend food shelf life is contributing to this imbalance (11).

Vegetable oils, which are rich in omega-6 fats, provide a large portion of the fat in the modern diet. Grain-fed animals, particularly dairy cows, and farmed seafood are thought to have lower levels of omega-3 fats (12).

Despite the widespread belief that a person should not consume more than three grams of omega-3 fatty acids per day, dose-ranging studies are necessary to determine the ideal intake, which may vary depending on factors including age, weight, and the severity of the illness (13).

The current research on omega-3 supplementation in ASD is summarized in this systematic review, with an emphasis on how it affects biological, behavioral, and cognitive results. The importance of omega-3 fatty acids for brain development and function has drawn attention to their possible therapeutic use in addressing these underlying mechanisms (14). EPA and DHA are long-chain polyunsaturated fatty acids (PUFAs) that make up omega-3 fatty acids. Neurotransmitter activity, neuronal membrane fluidity, and anti-inflammatory signaling all depend on these lipids (15). Clinical trials have been conducted to examine the potential advantages of supplementing after observational studies revealed that people with ASD had decreased omega-3 levels. The purpose of this review is to examine the effectiveness of omega-3 supplementation in ASD by combining data from observational studies, randomized controlled trials (RCTs) with an emphasis on biological, behavioral, and cognitive outcomes (16).

There are no cures for ASD, and although some interventions may help with some symptoms, they do not completely eliminate them. Additionally, when using medication, there may be unfavorable side effects like depression, weight gain, insomnia, withdrawal symptoms, and prolonged seizures (17). When trying to discover a cure for their child,

parents of children with ASD frequently act desperate. The fact that 74% of children with ASD use complementary and alternative medicines (CAM) compared to 12% of typically-developing children shows how persistent parents are in their search for alternative modalities (18). The majority of these treatments lack solid evidence, which could result in the ongoing use of a hazardous or inefficient treatment. One complementary and alternative medicine that has recently drawn increased attention is fatty acid supplementation, as research indicates that people with ASD may be deficient in certain fatty acids. To evaluate the possible advantages and disadvantages of this therapy, a comprehensive analysis of RCTs analyzing the impact of omega-3 fatty acids on ASD treatment is required.

Materials and Methods

Search Criteria

Studies published between 2010 and 2023 were covered by a thorough search of databases including PubMed, Embase, Cochrane Library, and Scopus. The following keywords were used: "autism spectrum disorder," "ASD," "omega-3," "EPA," "DHA," and "supplementation."

Search Procedures

The PICO methodology—participants (P), interventions or exposures (I), comparison (C), outcome (O), and study design (S)—was used to establish the screening criteria for the literature. P: Individuals with ASD who meet the DSM-IV, DSM-5, ADOS, or ADI-R diagnostic criteria.

I: Research on the effects of omega-3.

C: a lack of omega-3 fatty acids or control group.

Result: Symptoms associated with ASD have subsided.

Study design is randomized controlled trial.

Using their own pre- and post-control, the trial was split into two groups: the omega-3 control group and the observation group. These groups were well-balanced and comparable to one another. Stereotyped conduct, speech, social contact, and communication were among the things that were observed in at least one instance.

Exclusion criteria include: 1. Reviews, case studies, and research on animals.

2. Research looking examined the use of Omega-3 supplements in conjunction with

other therapies.

3. Research with imprecise or ambiguous outcome measures.

Data Analysis

1. Data extraction and study selection: carried out separately by a reviewer.

2. Using the Cochrane Risk of Bias Tool to assess risk of bias.

3. Data synthesis: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes are used in a random-effects model.

Outcomes

The main result is a change in the symptoms of ASD as assessed by standardized measures (such as the Social Responsiveness Scale and the Autism Diagnostic Observation Schedule).

2. Secondary outcomes: Modifications to quality of life, emotional control, and cognitive function.

Implications

The goal of this systematic review is to present a thorough summary of the data currently available about the effectiveness of omega-3 fatty acid supplements in reducing symptoms of ASD. The results will educate families, researchers, and medical professionals on the possible advantages and drawbacks of omega-3 supplementation for people with ASD.

Quality Appraisal and Data Extraction

The researcher collected 10 works of literature after independently assessing the caliber of the chosen literature and deciding which works should be included and which should be excluded. The Cochrane Collaboration Network's risk assessment scale for randomized controlled trials served as the foundation for the quality evaluation of the collected literature.

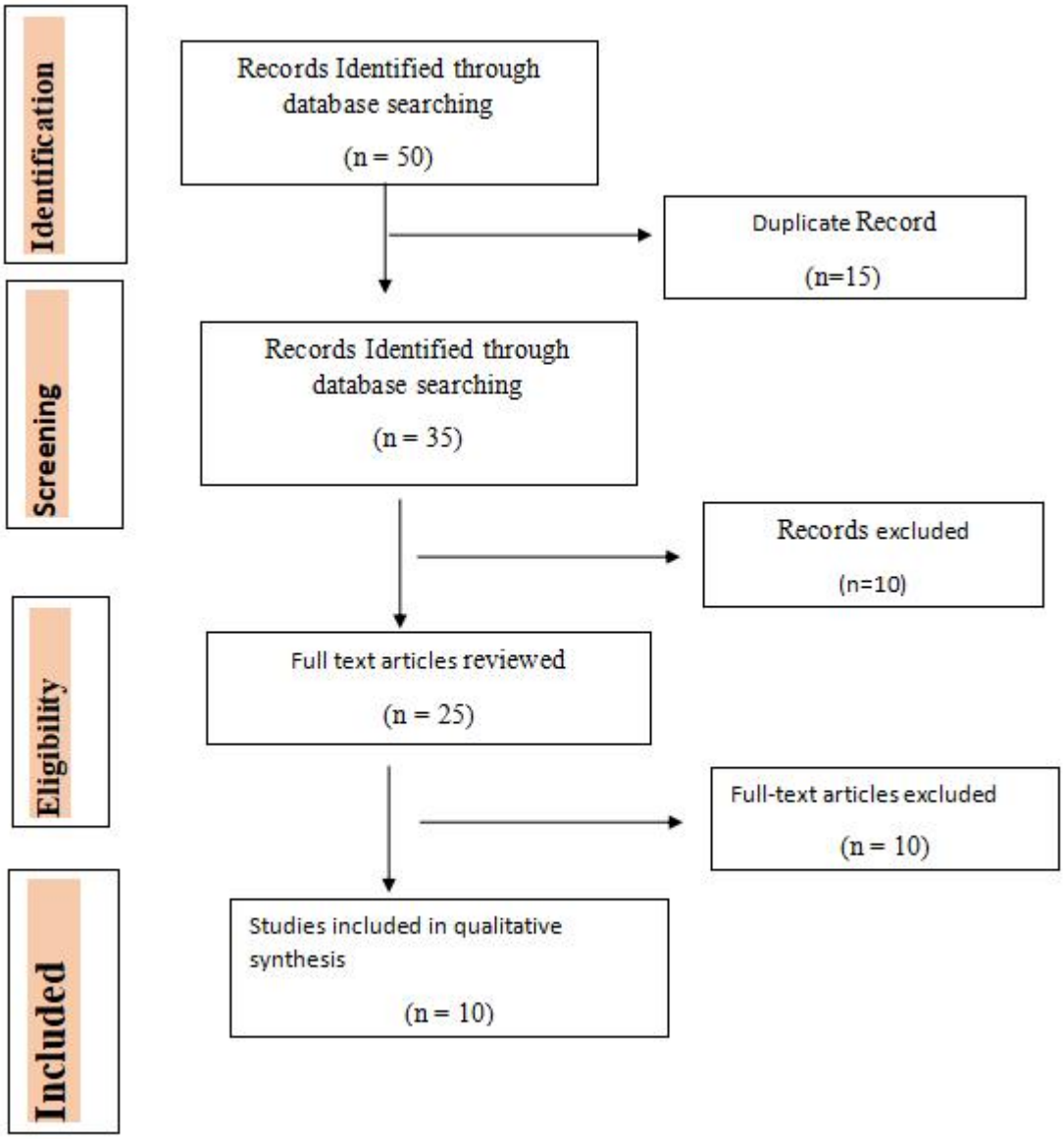
A researcher separately extracted the data. Data on the social, behavioral, and verbal treatment effects of patients with ASD in each literature was extracted, along with basic information about each one, such as the author, year, country, age, sample size, diagnostic criteria, intervention time, measurement tools, experimental reagents, and outcome indicators.

Results

Summary of Studies

There were 10 papers in all, all of which used open, double-blind, randomized clinical trial research with a sample size of 13–67 and 375 study participants. USA, Iran, Austria, Canada, Japan, Switzerland, Spain, and Italy are among the eight nations represented in the study. Three American studies, one Iranian study, one Switzerland, one Canada, one Austria, one Italian and one Japan study. The trial lasted between 6 weeks and 12 months, with omega-3 therapies lasting between 6 weeks and 6 months. All subjects were ASD patients, ages 2 to 40.

To confirm the diagnosis of ASD patients (n = 19), the majority of the included studies used the DSM scale, the ADOS scale (n = 3), the SCQ questionnaire (n = 3), and the Wechsler Intelligence Scale (n = 2). There are studies that use the ABC scale (n = 12), SRS scale (n = 8), GARS scale (n = 7), CGI scale (n = 4), and BASC scale (n = 3) to evaluate social, behavioral, and speech functioning in adults with ASD.



Flow Diagram For Paper Selection

Core Signs of ASD

The effects of omega-3 on the three primary symptoms of ASD—social interaction, behavioral function, and speech function—were examined in each of the studies.

Social Interaction

The SRS scale was primarily used in eight studies that looked at how omega-3 fatty acids affected social function in individuals with ASD, including social awareness, social

cognition, social communicative competence, social motivation, and autistic behavioral patterns. The SRS scale was employed in four of the research on omega-3 interventions. According to the Ooi study, participants evaluated using the SRS scale exhibited notable changes in social perception, social cognition, social communication, social motivation, autistic behavioral patterns, and overall scores following a 12-week omega-3 intervention. After using omega-3 supplements for 16 weeks, Yui's social communication significantly improved. The in vivo metabolic cycle of omega-3 was not further explained to guarantee that the elution duration was sufficiently long, despite the fact that the researchers established an effect removal time of two weeks to avoid consecutive effects. Parellada did not demonstrate an improvement in overall social functioning following omega-3 supplementation. However, the study also noted that Parellada used a crossover design and that there could be a sequential effect during the treatment phase, which would confound the treatment effect. After taking omega-3 supplements for six weeks, Bent and others did not exhibit any improvement in their social skills.

Behavioral Functioning

Behavioral functioning was evaluated using the ABC scale, the GARS, the CBCL, and the BASC system.

Checklist for Aberrant Behavior

Ten studies that employed the ABC scale looked at how omega-3 affected the five characteristics of abnormal behavior in individuals with ASD: incorrect speech, hyperactivity, lethargy/social behavior, irritation, and stereotypical behavior (19). Using the parent-rated version of the ABC scale, Bent demonstrated that subjects' tiredness and stereotypical behavior significantly (20). In 2011, Bent demonstrated no impact on the patients' aberrant conduct after consuming omega-3 for 12 weeks. Omega-3 in patients with ASD was the subject of two controlled clinical investigations by Stephen Bent in 2011 and 2014, respectively (20). The observation group and the control group in the 2011 trial were identical. There was no difference on the ABC scale. The inclusion of too few patients (n = 25) to assess efficacy was thought to be one of the possible causes of this analysis. Yui demonstrated that following 16 weeks of omega-3

supplementation, the observation group's social withdrawal significantly improved in comparison to the control group (21).

According to Amminger, a repeated measures ANOVA revealed no significant difference between the observation group and the control group following six weeks of omega-3 supplementation; nonetheless, there was a propensity for the observation group to experience a remission of symptoms related to hyperactivity (22). Following six months of omega-3 supplementation, Voigt demonstrated that there was no discernible difference between the control group and the observation group (23).

Children's Behavior Evaluation System

Three studies that also examined omega-3 supplementation assessed children's behavior using the BASC approach. In order to provide a thorough evaluation of children's behavior utilizing a variety of assessors, the BASC system is separated into self-reported, parent-rated, teacher-rated, and student-observed versions. After six months of the omega-3 intervention, Voigt employed teacher- and parent-rated assessments, and the observation group's social and communicative functions differed significantly from those of the control group (23). There was no discernible difference between the observation and control groups in Mankad's study conducted six months later using the parent-rated versions, which were observed at baseline, week 12, and week 24 (24).

Although Bent did not say which BASC system version was employed, there was no discernible change between the pre and post intervention periods (25).

								Experimental supplement		Scale score	
S.No	Intervention	Sample size	Age (yrs)	Literature (Country)	Intervention Time	Diagnostic Criteria	Measurement Tool	Experimental Group	Placebo Group	Experimental Group	Placebo group
1.	Omega-3	25	3–8	Bent et al. (20) USA	12 weeks	ADOS, DSM-IV,Expert clinicians, SCQ>12	CGI-I, BASC ABC	Pudding packets with an orange taste (EPA 350 mg and DHA 230 mg)	safflower oil in orange-flavored pudding	No improvement	No improvement
2.	Omega-3	41	7–18	Ooi et al. (26) Switzerland	12 weeks	Child psychiatrist [autistic symptoms rating at least moderate	CBCL, SRS, Blood status	One gram of omega-3 per day (DHA	Not mentioned		No improvement

						severity (CGI)], WPPSI,WIS3. C-IV,DSM-IV,		840 mg, EPA 192 mg, 15 milliliters of liquid Efamol Efalex per day, and 1,278 mg of pure evening primrose oil)		
3.	Omega-3	67	5–17	Parellada et al. (27) Spain	18 weeks	Child psychiatrist, DSM IV diagnosis of Pervasive	PUFAsTAS, SRS, CGI-S	964.1 mg for patients ages 5–	Vitamin E and liquid paraffin	No improvement	No improvement

		Developmental Disorder	11 (EPA 577.5 mg + DHA 385 mg + Vitamin E 1.6 mg); 1157.01 mg for patients ages 12–17 (EPA 693 mg + DHA 462 mg + Vitamin E 2.01 mg).

4.	Omega-3	19	18–40	Politi et al. (28) Italy	6 weeks	A doctor and a psychologist, DSM-IV 、WAIS	PDDBI, BASC-2, PLS-4, CGI-I, omega-3	EPA + DHA 0.75 g (1.875 mL once daily) for the first two weeks, then doubled to 1.5 g (3.5 mL) after that.	Medium chain triglycerides and refined olive oil were present in the placebo.	No improvement	No improvement
5.	Omega-3	13	5–17	Amminger et al. (28) Austria	6 weeks	No mentioned diagnostician ,DSM-IV	The Rossago Behavioral Checklist (individual	Two fish oil supplement gelatin	Not mentioned	No improvement	No improvement

								correspondence)	capsules with 0.93 g of EPA and DHA		
6.	Omega-3	48	3–10	Voigt et al. (23) USA	6 months	An experienced clinician, DSM-IV, CARS⩾30	ABC		1.5 g/day of omega-3 (EPA 0.84 g/day, DHA 0.7 g/day)	One gram of coconut oil (containing one milligram of vitamin E and one milligram of fish oil)	No improvement	No improvement

7.	Omega-3	13	6–28	Yui et al. (23) Japan	16 weeks	2 independent psychiatrists, DSM IV 、 WISC-IV > 80	ABC, SRS, Biomarkers: PUFAs (DHA,ARA); Transferrin; SOD	6 capsules a day (240 mg) containing ARA 、 DHA	120 mg daily, Aravita containing olive oil capsule	ABC-Social withdrawal (P < 0.01), SRS-Communication (p < 0.05)	No improvement
8.	Omega-3	54	5–15	Doaei,et al. (29) Iran	8 weeks	Clinician , ADOS、DSM IV	BMI, FFQ, GARS	1 g/d (180 mg EPA + 120 mg DHA)	1 g/d (medium chain triglyceride)	GARS-stereotyped behaviors (p = 0.02), GARS-social communication (p = 0.02), GARS-total score (P = 0.001)	No improvement

9.	Omega-3	57	5–8	Bent et al. (25) USA	6 weeks	ABC-H > 20, SRS, CGI-I	ABC-H > 20, SRS, CGI-I	Pudding packets with an orange taste (EPA 350 mg and DHA 230 mg)	The pudding with an orange taste contained safflower oil.	Parent ratings for ABC-lethargy (p = 0.01) and ABC-stereotypy (p = 0.05)	No improvement
10.	Omega-3	38	2–5	Mankad et al. (24) Canada	6 months	No mentioned diagnostician, DSM-IV	PDDBI, BASC-2, PLS-4, CGI-I	First 2 weeks, EPA + DHA 0.75 g (1.875 mL once a day), after 2 weeks,	Placebo contained refined olive oil and medium chain triglycerides	No improvement	No improvement

		the dose was doubled to 1.5 g (3.5 mL

1.DSM-IV, Diagnostic and Statistical Manual of Mental Disorders ; 2.TAS, Otal Antioxidant Status; 3.SRS, Social Responsiveness Scale; 4.CGI, Clinical Global Impression; 5.WISC-IV, Wechsler Intelligence Scale for Children; 6.WPPSI, The Wechsler Preschool and

Primary Scaleof Intelligence; 7.CBCL, Child Behavior Check List; 8.ADOS, The Autism Diagnostic Observation Schedule; 9.SCQ, Social Communication Questionnaire; BASC, Behavior Assessment System for Children; ADI, Autism Diagnostic Interview;

The abbreviations ABC, PDDBI, and CDI stand for Aberrant Behavior Checklist, Preschool Language Scale, Wechsler Adult Intelligence Scale, Treatment Emergent Symptom Scale, GARS, Gilliam Autism Rating Scale, DD-CGAS, The Developmental Disabilities — Children's Global Assessment Scale, and Sensory Processing Measure, respectively.

Checklist for Child Behavior

Children's behavioral issues and social abilities are evaluated using the CBCL in omega-3 supplementary research. Ooi's study, which employed a parent-reported version, demonstrated improvement in patients' social and attention issues and a significant difference between the observation groups' and control groups' findings (26).

Gilliam Autism Rating Scale

The GARS scale, a standardized instrument for evaluating severe behavioral abnormalities, including autism spectrum disorders, was utilized in some studies.

Following an 8-week omega-3 intervention, Saeid Doaei shown a significant improvement in GARS stereotyped behavior, social communication, and overall scores in the observation group (29). Children in the omega-3 group only showed substantially lower ratings for visual reaction, auditory response, and anxiety response when compared to the placebo group ($p < 0.05$).

Clinical Global Impression

Though the CGI-I scale was thought to be the most widely used metric in all clinical trials of patients with ASD to assess clinical outcomes, the results of five articles that used it to measure clinical outcomes—all of which were omega-3 supplemented studies—showed no discernible differences before and after the intervention.

Speech Function

Mankad evaluated the language proficiency at the start and 24 weeks using the PLS (Preschool Language Scale) (24). The study's findings, however, indicated that there was no discernible difference between the control group and the observation group (24). Using linear regression in the statistics, Mankad's language assessment was carried out at the start and finish of the study; there was no follow-up phase.

Discussion

Considering the food selectivity of individuals with ASD and the lack of effective medications for treating the disorder, some research is progressively examining nutritional therapy as a means of making up for nutritional deficiencies and reducing core symptoms (30) . Of the various nutritional therapies, fatty acid supplementation stands out. The findings of the literature varied among the ten research that examined the effects of omega-3 supplementation in individuals with ASD. The Ooi study was the

best, although only a small number of the trials demonstrated that supplements were useful in reducing the main symptoms linked to ASD. However, the Ooi study was of relatively low quality, with two high risk ratings and two unknown risk assessments (26).

The success of the study is significantly impacted by adherence to nutritional recommendations. Research has indicated that a high level of adherence to family interventions for ASD improves a patient's IQ, eases symptoms, and streamlines treatment delivery (31). The success of trials on omega-3 supplementation in patients with ASD is directly impacted by patient adherence control. The strategy to adherence control used in the literature reviewed in this analysis also differed. In order to track patient adherence, Parellada asked patients to turn in all omega-3 capsules, whether they were empty or not, along with a weekly calendar (31). The researcher also counted the number of prescriptions. In order to monitor patient adherence and adverse events, a researcher additionally performed telephone assessments every other week during the intervention. Weeks two and eight saw a phone call to Bent, week six saw a quick evaluation, and week twelve saw a final visit. In his 2014 trial, Bent employed an internet-based random controlled trial methodology (25). 863 registered members were contacted in advance via email, and interested parents were asked to fill out a screening questionnaire by clicking on an embedded link in the email. Additionally needed is a parent, guardian, or educator who is willing to fill out the baseline data and assessment by email. Parents of children who have undergone eligibility screening fill out an online informed consent form by signing an electronic signature. Stereotypical conduct, communication problems, social interaction problems, the protracted nature of the illness, the high expense of therapy, the strain on families, and the psychological toll on caregivers are all symptoms that patients with ASD must deal with. Adherence with ASD is significantly impacted by these characteristics, and patients can regain their social functioning with additional strategies to improve patient compliance management (25).

The analysis discovered that Bent lost one patient in 2011 but none in 2014. Additionally, it is evident that a multi-path, internet-based intervention strategy can improve patient adherence. The necessity of long-term interventions for patients with ASD is mentioned in the current expert consensus and guidelines for the management of these patients (32). Treatment adherence is a crucial metric in intervention studies and a foundation for

guaranteeing the efficacy of long-term treatment for patients with ASD. Children and adults with ASD often have higher levels of interleukin-1β in their plasma (33). It has been demonstrated that ASD and cognitive function are linked to mutations and polymorphisms in IL-1β and its receptor (34).

According to the results, if the intervention itself has an immunomodulatory effect, participants with greater levels of inflammation are immune responders; if the intervention has no immunomodulatory effect, however, they are not inflammation-responsive. According to studies, patients with ASD have immunological changes in their peripheral blood and CSF fluid (33), which are accompanied by increases in pro-inflammatory cytokines like IL-1α and β, IL-1Ra, IL-4, IL-6, IL-10, TNF-α, and IFN-γ (35). Based on this, one could hypothesize that omega-3 could alleviate ASD's clinical symptoms by reducing inflammation (36). The same team of researchers conducted both studies, however study delves deeper into the impact of pretreatment inflammatory status changes on the therapeutic outcomes of omega-3 intervention (37). Prior to the study, baseline data on participants' inflammatory status (IL-1ra, IL-6, and hs-CRP) were included, and inflammatory status stratification was carried out. The results indicated that participants with higher levels of inflammation had better treatment outcomes than the placebo group.

It should be mentioned that there are negative effects linked to omega-3 supplementation. Parellada (27) found that the only notable side effect after the intervention was a little rise in total cholesterol during the study. Five participants in the observation group of the Bent (20) research reported the following adverse events: two rashes, one upper respiratory tract infection, one nosebleed, and one worsening of gastrointestinal problems. Nevertheless, the control group also experienced four negative events: three increases in hyperactivity and one increase in self-stimulatory behavior. The observation and control groups did not differ significantly from one another. Amminger shown that although the control group experienced headache and insomnia, the observation group experienced moderate adverse effects including fever (22). Aside from this, there were a few minor side effects, but there was no discernible difference between the observation and control groups. The prevalence of side effects such gastrointestinal issues (vomiting, diarrhea) is concerning.

Researchers verified study preconceptions in many studies on the same research topic, according to our findings. The same research team conducted two experimental trials in 2011 and 2014, respectively. In order to ascertain the viability, initial safety, and effectiveness of omega-3 for the treatment of ADHD in children with ASD, a pilot randomized controlled study was carried out in 2011 (20). Following 12 weeks of therapy, there was a positive link between lower fatty acid levels and lower ADHD levels, and the treatment was well received. Nevertheless, omega-3 fatty acids had no statistically significant impact on the main symptoms of autism or ADHD.

In 2014, a novel internet-based clinical trial design was carried out, and the results indicate that internet-based randomized controlled trials of therapies for children with ASD are possible and could result in a notable decrease in trial completion time and expense (25).

Though a trend toward a non-significant positive effect was noted, omega-3 fatty acids did not significantly lower ASD symptoms.

Despite the fact that we chose several people with evidence-based experience to evaluate each other independently when searching the evaluation literature, this study has several limitations. These include the small amount of literature included in the study, the small number of subjects compared to the observation group, the fact that the studies were not methodologically consistent with one another, and the possibility of assessment bias. Standardized studies on the timing and amount of omega-3 supplementation are lacking, as is high-quality research on omega-3 in patients with ASD. According to evidence-based reasoning, the recommended reference quantity for the usual omega-3 supplementation dose for patients with ASD is EPA + DHA at a combination of 1.3–1.5 g/day for 16–24 weeks. Future multicenter studies with sizable sample sizes are advised in order to confirm the dosage and supplementation strategy that will help people with ASD alleviate their symptoms.

Conclusion

This review methodically looked at the existing research on omega-3's ability to alleviate the main symptoms of ASD. According to the review, using omega-3 supplements did not significantly improve ASD symptoms and was insufficient to indicate that the main symptoms had been reduced. Patients with ASD who took omega-3 supplements

experienced improvements in behavioral functioning and other key symptoms of the disorder. The findings of the literature that was part of this investigation, however, were a little inconsistent. To better understand how omega-3 works in patients with ASD, more thorough research is required.

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