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Impact of Omega-3 Fatty Acids Supplementation on Clinical Manifestations in Autism Spectrum Disorders: An umbrella review of meta-analyses

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition. Omega-3 fatty acids insufficiency has been linked to ASD. This umbrella meta-analysis was performed to investigate the effects of omega-3 supplementation on clinical manifestations in participants with ASD. Based on PRISMA statement, databases including Web of Science, PubMed, and Scopus were systematically searched for published meta-analyses on the effect of omega-3 supplementation on ASD. To assess the risk of bias, the assessment of multiple systematic reviews (AMSTAR)-2 was utilized. The outcomes were core and non-core symptoms of ASD including social withdrawal/lethargy, cluttering speech, hyperactivity, irritability, and stereotypy. Seven meta-analyses eventually remained in the umbrella review. The results revealed that omega-3 fatty acids supplementation caused a significant reduction in cluttering speech in studies conducted on age ≤8 years (ES= -0.30; 95% CI: -0.55, -0.06; *P*=0.02). Omega-3 supplementation caused a significant reduction in hyperactivity in participants ≤8 years (ES= -0.30; 95% CI: -0.55, -0.06; P=0.02) and in participants who received the supplements for more than 14 weeks (ES= -0.30; 95% CI: -0.55, -0.06; *P*=0.02). A dosage of ≤1000 mg/d of omega-3 supplementation led to a significant increase in the stereotypy/ restricted and repetitive interests and behaviors (ES= 0.19; 95% CI: 0.03, 0.35; *P*=0.02). This umbrella review revealed that omega-3 fatty acid may be a beneficial supplement to control cluttering speech and hyperactivity in children lower or equal to 8 years old with ASD.

Keywords: Autism spectrum disorder; omega 3; cluttering speech; irritability; hyperactivity; stereotypy; umbrella meta-analysis

Introduction

Autism Spectrum Disorder (ASD), which is increasingly being known as Autism Spectrum Condition (ASC), is a neurodevelopmental condition distinguished by restricted and repetitive interests and behaviors (RRIB), and also challenges in social interaction and communication (1). In addition to the complications of autistic children, parents of autistic children have several family conflicts due to care demands, mental health challenges, difficulties with community integration for their children, and financial issues of autism-related costs (2). The prevalence of ASD has been increased globally, with an estimated prevalence of 100 out of every 10,000 people in 2022 (3). Despite extensive investigation, the exact etiology of ASD remained unclear, with a consensus pointing towards a complex interplay of genetic alterations, maternal obesity, diabetes or immune system disorders, maternal history of smoking, alcohol, substance abuse (4-7), preterm birth, birth difficulty leading to periods of oxygen deprivation to the baby's brain, fever/infections, altered zinc-copper cycles, which regulate metal metabolism in the body, and environmental factors such as diet and prenatal exposure to contaminants (8-12). Moreover, the association between ASD and these risk factors can be influenced by dietary components. For example, the relationship between ASD and maternal smoking appears to be mediated by low maternal fish consumption.

In recent years, there is an increasing focus on the impact of dietary intervention on the development and management of ASD (13). Among these, omega-3 fatty acids, particularly very long-chain polyunsaturated fatty acids (LC-PUFAs) found in fish oil and certain plant oils, have gained more attention (14). Omega-3 fatty acids as crucial components of brain play a significant role in the development and functioning of the brain (15). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as two types of very LC-PUFAs are vital for maintaining the fluidity of cell membranes, facilitating communication between neurons, and supporting the growth and repair of brain tissue. Moreover, the anti-inflammatory properties of omega-3 fatty acids may improve neuroinflammation, which is considered as a pathogenic mechanism for neurological disorders (16). Furthermore, the neuroprotective effects of omega-3 fatty acids are thought to be beneficial in preserving brain function and preventing cognitive decline (17).

Children with ASD were reported to have low blood concentrations of omega-3 LC-PUFAs (18, 19). Several studies investigated the effects of omega-3 supplementation in individuals with ASD (20-23). These investigations are varied widely in terms of methodology, dosage,

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composition of omega-3 used, and duration of supplementation (21, 24) and their results were contradictory, some studies reported improvements in symptoms such as hyperactivity (25, 26), communication (27), and social interaction (28), while some others found no significant effects (26, 28, 29). So, the present umbrella review of meta-analysis was executed to assess the clinical effectiveness of omega-3 supplementation in improving ASD symptoms.

Methods

This umbrella review of meta-analyses was executed utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (30). The protocol of this meta-analysis was registered in PROSPERO (ID: CRD42024498733).

Search strategy

From 1990 up to December 2023, three international databases including PubMed, Scopus, and Web of Science were systematically searched for the existing meta-analyses on the omega-3 supplementation in participants with ASD. The search strategy was developed using the following Medical Subject Heading (MeSH) terms and keywords: ((((((("Fatty Acids, omega-3"[Mesh]) OR "Eicosapentaenoic Acid"[Mesh]) OR "Docosahexaenoic Acids"[Mesh]) OR "Linolenic Acid"[Mesh]) OR (((((((("omega 3"[Title/Abstract]) OR ("omega-3 fatty acid"[Title/Abstract])) OR ("Eicosapentaenoic Acid"[Title/Abstract])) OR ("Docosahexaenoic Acids"[Title/Abstract])) OR ("Linolenic Acid"[Title/Abstract])) OR ("lipoic acid"[Title/Abstract])) OR ("ethyl-eicosapentaenoic acid"[Title/Abstract]))) AND ((("Autism Spectrum Disorder"[Mesh]) OR "Child Development Disorders, Pervasive"[Mesh]) OR ((((((("autism"[Title/Abstract]) OR ("autism spectrum disorder"[Title/Abstract])) OR ("ASD"[Title/Abstract])) OR ("Asperger"[Title/Abstract])) OR ("Pervasive development disorder"[Title/Abstract])) OR ("PPD"[Title/Abstract]))))) AND ((("Systematic Review" [Publication Type]) OR "Meta-Analysis" [Publication Type]) OR (("Systematic Review"[Title/Abstract]) OR ("Meta-Analysis"[Title/Abstract])))). Additionally, to enhance the sensitivity of search strategy, the wild-card term "*" was used. The entire search strategy is described in Supplementary Material 1.

Eligibility criteria

In this meta-analysis of meta-analyses, the studies with following conditions were included: (1) systematic review and meta-analysis; (2) publications exploring the effect of omega-3 supplementation in participants with ASD. Observational studies, quasi-experimental studies, case reports and case-series, animal studies, letters, reviews, and commentaries were

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excluded from the analysis. The PICO of this umbrella review was as follows: Population/Patients (P: participants with ASD); Intervention (I: omega-3 fatty acids supplementation); Comparison (C: placebo or standard treatment); Outcome (O: social withdrawal/lethargy, cluttering speech, hyperactivity, irritability, and stereotypy/RRIB).

Methodological quality assessment

The included meta-analyses were assessed by one of the researchers (H.A) and checked by the second author (S.D). To assess the risk of bias, the assessment of multiple systematic reviews (AMSTAR)-2 was utilized. This tool is designed to assess the quality of systematic reviews which has 16 items with 7 critical domains (containing items 2, 4, 7, 9, 11, 13, and 15) answering with a "No meta-analysis" or "No" or "Partial Yes" or "Yes" operators. Overall quality is rated as "Critically low", "Low", "Moderate", and "High" (31).

Data extraction

The acquired data was extracted by one of investigators (F.B) and checked by another researcher (H.A). The publication year, country, the included studies, study duration, quality assessment scales, the outcomes, and the first author of the study and participants' characteristics encompassing sample size, age, range and mean of dosage of omega-3 supplementation in randomized controlled trials (RCTs) were inserted in a predesigned Microsoft World table.

Data synthesis and statistical analysis

For statistical analysis with effect sizes and confidence intervals, random-effects restricted maximum likelihood model was utilized to execute this umbrella meta-analysis. Using the I^2 index, between-study heterogeneity was evaluated. Generally, I_2 index exceeding 50% was considered as a high heterogeneity (32). Subgroup meta-analysis was conducted considering sample size, study duration, age, the included articles, dosage, and the study quality to identify the sources of potential heterogeneity. For estimating the impact of each study on the pooled effect size of the meta-analysis, sensitivity analysis considering the Leave-one-out Method was performed. The funnel plot inspection and Begg's rank correlation and Egger's weighted regression tests were conducted to identify any publication bias (33, 34). In cases of publication bias, Duval & Tweedie "trim and fill" analysis was performed. STATA version 16 (Stata Corporation, College Station, TX, US) was used for all statistical analyses with considering a significant level of $P < 0.05$.

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Results

Study selection

Meta-analysis of RCTs with publication years ranging from 2011 to 2021 were included in the present study. As shown in Figure 1, through the initial systematic searches, 99 eligible articles were retrieved. After removing duplications, 76 records were screened in the title/abstract's evaluation phase, of which 60 papers were excluded. Afterwards, based on the research topic, 16 studies were obtained for assessing full-text, of which 9 studies were excluded because of miscellaneous reasons including one systematic review without meta-analysis (35), one study in various populations (36), two irrelevant articles (14, 37), and five studies that had no data of interest (21, 29, 38-40).

Demographic characteristics of the included studies

The characteristics of the included articles are presented in Table 1. The combined sample size in these meta-analyses was 1398 participants. The sample size varied from 40 to 405. The average age of meta-analyses was 7.68 years. Of 7 meta-analyses selected, two studies were executed in the United states (41, 42), one study in China (26), one study in New Zealand (22), one study in Poland (43), one study in Spain (44), and one study in United Kingdom (38). Seven meta-analyses evaluated the impact of omega-3 supplementation on social withdrawal/lethargy (n= 6), cluttering speech (n= 6), hyperactivity (n= 6), irritability (n= 6), and stereotypy/ repetitive and restricted interests and/or behaviors (RRIB) (n= 7). In addition, some studies evaluated other outcomes containing internalizing, externalizing, functional communication, adaptive skills, cognition, aggression, quality of sleep, self-harm, and attention.

Results of methodological quality assessment

Based on the AMSTAR-2, the findings of the quality assessment are shown in Table 2. From seven meta-analyses of RCTs, one meta-analysis was of high quality (42), four were low quality (22, 38, 41, 43), and two were critically low quality (26, 44).

Effect of omega-3 fatty acid supplementation on social withdrawal/lethargy

The six meta-analyses that reported the impact of omega-3 on social withdrawal/lethargy were entered into this umbrella meta-analysis (Fig. 2A) and the results indicated no significant impact of omega-3 on social withdrawal/lethargy in ASD participants (ES= -0.22; 95% CI: -0.78, 0.35; P= 0.45). However, a significant between-study heterogeneity was observed (I^2 = 76.86%, P<0.001). The evidence of small-study effect was not observed (Egger's (P=0.32) and Begg's tests (P=1.00). Publication bias analysis demonstrated that the

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shape of funnel plot was asymmetric (Fig. 3A). Moreover, trim and fill analysis, which is a method based on the addition of studies to the funnel plot so that it becomes symmetrical aimed at both identifying publication bias and adjusting results for it, was performed with six studies and found no publication bias (ES= 0.04; 95% CI: -0.15, 0.22; *P*>0.05).

Effect of omega-3 fatty acid supplementation on cluttering speech

Cluttering is another language problem found in autism that can result in fast, unclear conversations Some signs of cluttering speech include rapid talk, syllables that run together, excessive filler words and repetitions, and abnormal pauses (45). Cluttering may be caused by a combination of genetic factors, neurological differences, and language development issues (46). As shown in Figure 2B, the overall effect size from six studies indicated that there was no significant link between omega-3 supplementation and cluttering speech in participants with ASD (ES= -0.22; 95% CI: -0.78, 0.35; *P*= 0.45). Although, there was a significant between-study heterogeneity (I^2 = 76.86%, *P*<0.001). Subgroup analysis according to the age revealed that cluttering speech was significantly reduced in studies conducted on age ≤8 years (ES= -0.30; 95% CI: -0.55, -0.06; *P*=0.02) (Table 3). The significant small-study effects with performing Egger's and Begg's tests was assessed (*P*=0.32 and 1.00, respectively). However, visual inspection of funnel plot showed an asymmetric shape (Fig. 3B). The trim and fill analysis found no publication bias (ES= 0.04; 95% CI: -0.15, 0.22; *P*>0.05).

Effect of omega-3 fatty acid supplementation on hyperactivity

The results of this umbrella meta-analysis indicated that there was no significant effect of omega-3 on hyperactivity in participants with ASD (ES= -0.13; 95% CI: -0.48, 0.22; *P*>0.05) (Fig. 2C), although a significant between-study heterogeneity was observed (I^2 = 45.60%, *P*=0.05). After subgroup analysis based on age and study duration, there were significant reductions in hyperactivity in participants ≤8 years (ES= -0.30; 95% CI: -0.55, -0.06; *P*=0.02) and in participants who received omega-3 fatty acid supplementation for more than 14 weeks (ES= -0.30; 95% CI: -0.55, -0.06; *P*=0.02) (Table 3). The evidence of small-study effect was not observed (Egger's test *P*=0.61 and Begg's tests *P*=1.00). Publication bias analysis demonstrated that the shape of funnel plot was asymmetric (Fig. 3C). In accordance to that, the trim and fill analysis was performed with six studies and found no publication bias (SMD= ES= -0.13; 95% CI: -0.33, 0.07; *P*>0.05).

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Effect of omega-3 fatty acid supplementation on irritability

No significant effect of omega-3 on irritability was observed (ES= 0.09; 95% CI: -0.12, 0.30; *P*>0.05) (Fig. 2D) with a low between-study heterogeneity (I^2 = 0%, *P*=0.89). Regarding subgroup analysis, the result did not change. The Egger's (*P*=0.73) and Begg's (*P*= 1.00) tests found that the overall ES did not change by the exclusion of any individual study. Additionally, asymmetric shape of funnel plot confirmed presence of publication bias (Fig. 3D). The trim and fill method found no publication bias (ES: 0.09; 95% CI: -0.12, 0.30; P>0.05).

Effect of omega-3 fatty acid supplementation on stereotypy/RRIB

Based on 7 included papers, the results found no significant effect of omega-3 fatty acid supplementation on stereotypy/RRIB (ES= 0.01; 95% CI: -0.29, 0.31; *P*=0.95) (Fig. 2E) with high between-study heterogeneity (I^2 = 64.30%, *P*=0.01). After analyzing subgroups based on various dosages which were used in the included meta-analyses, the results showed that omega-3 fatty acid supplementation with a dosage of ≤1000 mg/d led to a significant increase in the stereotypy/RRIB (ES= 0.19; 95% CI: 0.03, 0.35; *P*=0.02) (Table 3). Small-study effect was not found using Egger's (*P*=0.45) and Begg's (*P*= 1.00) tests. The shape of funnel plot was not symmetric (Fig. 3E). By using trim and fill analysis, no publication bias was detected (ES: 0.01; 95% CI: -0.29, 0.31; P>0.05).

Discussion

This is the first umbrella review to clarify the effect of omega-3 supplementation in the ASD population. The results revealed that cluttering speech had a significant reduction in studies conducted on age ≤8 years. There were significant reductions in hyperactivity in participants ≤8 years and in participants who received omega-3 fatty acid supplementation for more than 14 weeks. No significant benefit was found regarding the effect of omega-3 supplementation on social withdrawal, lethargy, and irritability. Similarly, a recent review found that omega-3 fatty acids are ineffective for ASD symptoms, whereas omega-3 fatty acids combined with vitamin D may improve behavior and social interactions (14). In contrast, a 2017 study provided some evidence that omega-3 fatty acids may alleviate lethargy in children with ASD, as reported by parents in two different trials. However, these positive indications were in contrast to other trials that showed an increase in externalizing behaviors and a decline in social skills. Additionally, a review examining various nutritional interventions, including omega-3 supplements, found that while many studies reported improvements in the behavioral symptoms of children with ASD, the wide variability in outcomes across these

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studies precludes a definitive conclusion regarding the most effective nutritional intervention strategy (47).

Our study did not observe a significant effect of omega-3 on cluttering speech in all participants with ASD. Yet, when focusing on children aged 8 and younger, a subgroup analysis indicated significant improvements. This finding is in contrast to a meta-analysis of RCTs, which reported no effect of omega-3 on the symptoms of ASD, such as speech function (14). On the other hand, Bent et al. in a systematic review identified a wider array of benefits, with omega-3 supplementation linked to improvements in language and learning skills, suggesting that the supplement's effectiveness may vary across different domains and age groups (35).

Based on a meta-analysis, the prevalence of hyperactivity among ASL individuals is 38.5% (48). In our study, we found that omega-3 supplementation did not lead to a significant change in hyperactivity levels among the general population of ASD participants. However, positive effects were observed for specific groups including children aged 8 or younger and those who received omega-3 supplementation for more than 14 weeks. These results are in contrast to one meta-analysis of RCTs, which did not identify any benefits of omega-3 in reducing hyperactivity in ASD participants (22). Nonetheless, some individual studies suggest that omega-3 fatty acids may help alleviate hyperactive symptoms in people with ASD, highlighting the potential for omega-3 to be beneficial in particular contexts or subgroups within the ASD population (26).

In the present umbrella review, we found that omega-3 supplementation did not significantly reduce irritability in participants with ASD, as evidenced by the consistency of results across studies, shown by the low heterogeneity. This result remained unchanged even after performing subgroup analysis. This is in line with published meta-analyses of RCTs that reported no benefits from omega-3 in alleviating irritability in participants with ASD (22). However, there are conflicting reports; one study highlighted that omega-3 supplementation led to improvements in general health and behavior according to parental observations (35).

The results of the present study indicated that omega-3 supplementation had no effect of stereotypy or RRIB in individuals with ASD. This is in line with previous research, which concluded that omega-3 fatty acids did not significantly reduce RRIB in ASD (42). However, a small number of studies suggest that omega-3 may offer some benefit in improving symptoms of stereotypy in ASD (22, 26). Sub-group analysis of our research found that omega-3 supplementation with a dose of less than 1000 mg may increase the stereotypy or

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RRIB in individuals with ASD. These contradictory results may be due to the existing high heterogeneity and small sample size of the included meta-analyses and systematic reviews. In line with this result, a recent study on the association between maternal prenatal fish intake and child autism-related traits found that intake of some type of fish was associated with higher Social Responsiveness Scale (SRS) scores (indicative of higher levels of ASD traits) (49). It is possible that in low doses of omega-3 supplements extracted from fish oil, the effects of toxicants may outweigh the beneficial effects of omega-3. Also, in some studies, the exact type of omega-3 fatty acid was not specified, and different types of omega-3 fatty acids may have different effects on brain function (50).

Our comprehensive review on omega-3 supplementation and ASD was implemented with stringent methodology including a detailed search across databases, selection of the most extensive meta-analyses per outcome, and strict adherence to the inclusion criteria. Focusing exclusively on randomized controlled trials ensures strong and reliable causal inference regarding the effects of omega-3 fatty acids on ASD. However, the present study has some limitations. There was high heterogeneity across meta-analyses in terms of dosage, participant age, and study duration, which complicates the interpretation of results. The quality of some included studies has reported to be highly questionable. Variations in the methodological quality of included meta-analyses, from high to critically low, may affect the quality of the results obtained. The presence of publication bias, suggested by asymmetric funnel plots, indicates a potential overrepresentation of positive findings. Furthermore, the outcomes measured may not cover all relevant ASD symptoms. Small sample sizes in some studies may reduce statistical power, and differences in populations limit the generalizability of results. In addition, the severity of ASD, the type of omega-3 fatty acids, and the blood level of omega-3 fatty acids were not mentioned in the included meta-analyses and it was not possible to perform sub-group analyses based on the severity of the disease and different types of fatty acids. This review is also reliant on the risk of bias within primary studies. There is a lack of long-term effect data and possible underreporting of adverse effects. Future research on omega-3 fatty acids in ASD should prioritize large-scale, well-designed trials with long-term follow-ups to confirm the obtained results and strengthen the evidence base for public health practice. Future studies should standardize supplementation protocols and include diverse populations to enhance generalizability. A broader range of ASD-related outcomes should be assessed, and efforts to understand the biological mechanisms of omega-3 effects on ASD are needed. Reporting the adverse effects and ensuring all results are

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published will reduce publication bias, providing a clearer picture of the effect of omega-3 on ASD symptoms.

Conclusion

This umbrella meta-analysis revealed that omega-3 fatty acid supplementation may be beneficial to reduce cluttering speech and hyperactivity in children lower or equal to 8 years old with ASD. Also, omega-3 fatty acid may improve hyperactivity in participants who receive omega-3 fatty acid supplements for more than 14 weeks. Supplementation with omega-3 does not significantly impact other symptoms of ASD including social withdrawal, hyperactivity, and irritability. Further studies with longer duration and various dosage of different types of omega-3 fatty acids are required to illuminate these particular aspects and to discover the underlying mechanisms of the effects of omega-3 fatty acids on ASD symptoms.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary material.

Ethics approval

None.

Acknowledgments

None.

Author Contributions

H.A: systematic search; risk of bias assessment, preparing the figures; F.B, S.Kh: study selection, data extraction; AP, MGh: conceptualization, drafting the manuscript; S.D: conceptualization, supervision and critically editing the manuscript. All authors approved the final version for submission.

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Table 1. The characteristics of the included meta-analyses and systematic reviews.

Study, date	Included studies	Location, Duration	Participants (n)	Age (yrs)	Intervention (Range and mean of dose and duration)	Omega 3 type	Quality assessment scale	Outcomes
James et al. 2011 (40)	2	USA 2007-2011	40	8.1	650-1500 mg/d (1075 mg/d) 6-12 wks (9 wks)	DHA and EPA	Cochrane 5.5/8	-Social withdrawal/lethargy NS -Inappropriate speech NS -Stereotypy NS -Hyperactivity NS -Irritability NS
Cheng et al. 2017 (25)	6	China 2007-2015	194	7.7	200-1500 mg/d (1206.66 mg/d) 6-24 wks (14.7 wks)	NA	Jadad 4.67/5	-Hyperactivity NS -Lethargy S↓ -Stereotypy S↓ -Inappropriate speech NS -Irritability NS - Clinical Global Impression-Improvement NS -Social Responsiveness Scale NS -Dropout rate NS -Rate of discontinuation due to side effects NS
Mazahery et al. 2017 (21)	4	New Zealand 2007-2015	107	8.4	240-1540 mg/d (1025 mg/d) 6-16 wks (10 wks)	DHA and EPA	Health Canada Quality Appraisal Tool for Experimental Studies 11.5/15	-Social interaction S↓ -Communication scores NS - Repetitive and restricted interests and behaviors S↓ -Hyperactivity NS -Irritability NS
Horvath et al. 2017 (42)	5	Poland 2007-2015	183	6.7	200-1540 mg/d (1112 mg/d) 6-24 wks (14.4 wks)	DHA and EPA	Cochrane 6/8	-Irritability NS -Lethargy NS -Stereotypy NS -Hyperactivity NS -Inappropriate speech NS -Internalizing NS -Externalizing NS -Functional communication NS -Social skills NS -Behavioral NS -Adaptive skills NS

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								-CGI-I overall [NS] -Social awareness [NS] -Social cognition [NS] -Social communication [NS] -Social motivation [NS] -Autistic mannerisms [NS]
Fraguas et al. 2019 (43)	7	Spain 2007-2017	259	8.1	240-1500 mg/d (814.6 mg/d) 6-24 wks (13.7 wks)	NA	Cochrane 4.3/6	-Autistic general psychopathology [NS] -Global severity [NS] -Cognition [NS] -Hyperactivity and irritability [NS] -Language (general) [S ↓] -Social-autistic [S ↓] -Stereotypies and restricted and repetitive behaviors [NS]
De Crescenzo et al. 2020 (37)	9	United Kingdom 2007-2018	405	7.3	200-1500 mg/d (901.3 mg/d) 6-52 wks (18 wks)	EPA and DHA	GRADE 1.4/4	-Hyperactivity [NS] -Aggression [NS] -Irritability [NS] -Anxiety [S ↓] -Adaptive functioning [NS] -Social interaction [NS] -Restricted and repetitive interests and behaviors [NS] -Communication [NS] -Quality of sleep [NS] -Self-harm [NS] -Attention [NS] -Hyperactivity and disruptive behaviors [NS]
Zhou et al. 2021 (41)	5	USA 2007-2019	210	7.5	650-1500 mg/d (896.8 mg/d) 6-48 wks (16 wks)	NA	NA	-Restricted, repetitive and patterns of behaviors [NS]

N: number; Yrs: years; Wks: weeks; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; NS: non-significant; S: significant; GRADE: Grading of Recommendations Assessment, Development and Evaluation; NA: not available

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Table 2. Results of methodological quality assessment of the included meta-analyses via AMSTAR 2.

Study	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**	**Q15**	**Q16**	**Overall**
James et al. 2011 (40)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Low
Cheng et al. 2017 (25)	Y	N	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Critically low
Mazahery et al. 2017 (21)	Y	PY	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Low
Horvath et al. 2017 (42)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Low
Fraguas et al. 2019 (43)	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Critically low
De Crescenzo et al. 2020 (37)	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Zhou et al. 2021 (41)	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Abbreviations: Y, Yes; PY, Partially Yes; N, No; Questions: Q1- Did the research questions and inclusion criteria for the review include the components of PICO? Q2- Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol? Q3- Did the review authors explain their selection of the study designs for inclusion in the review? Q4- Did the review authors use a comprehensive literature search strategy? Q5- Did the review authors perform study selection in duplicate? Q6- Did the review authors perform data extraction in duplicate? Q7- Did the review authors provide a list of excluded studies and justify the exclusions? Q8- Did the review authors describe the included studies in adequate detail? Q9- Did the review authors use a satisfactory technique for assessing risk of bias (RoB) in individual studies that were included in the review? Q10- Did the review authors report on the sources of funding for the studies included in the review? Q11- If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results? Q12- If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13- Did the review authors account for RoB in individual studies when interpreting/discussing the review results? Q14- Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the review results? Q15- If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the review results? Q16- Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review

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Table 3. Subgroup analysis for omega-3 supplementation on outcomes in ASD participants.

Biochemical test	Effect size (number)	ESs (95% CI)	P-within	I^2(%)	P-heterogeneity
Hyperactivity					
Overall	6	-0.13(-0.48, 0.22)	0.45	45.60	0.05
Sample size (subjects)					
>110	4	-0.13(-0.47, 0.22)	0.48	56.82	0.10
≤110	2	0.42(-5.04, 5.88)	0.88	78.67	0.03
Duration (weeks)					
>14	3	-0.30(-0.55, -0.06)	0.02	0	0.80
≤14	3	0.13(-2.18, 2.45)	0.91	65.53	0.08
Age (years)					
>8	3	0.13(-2.18, 2.45)	0.91	65.53	0.08
≤8	3	-0.30(-0.55, -0.06)	0.02	0	0.80
Included articles					
>5	3	-0.13(-0.48, 0.22)	0.46	66.46	0.05
≤5	3	0.59(-3.28, 4.46)	0.77	58.70	0.08
Dosage (mg)					
>1000	4	-0.15(-1.88, 1.57)	0.86	40.69	0.17
≤1000	2	-0.03(-0.51, 0.46)	0.91	75.18	0.04
Quality					
Critically low	2	-0.06(-0.62, 0.50)	0.83	79.35	0.03
Low	4	-0.11(-1.83,	0.90	40.54	0.17

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		1.60)			
Inappropriate speech					
Overall	6	-0.22(-0.78, 0.35)	0.45	76.86	<0.001
Sample size (subjects)					
>110	4	-0.05(-0.50, 0.40)	0.83	72.94	0.01
≤110	2	-1.08(-3.61, 1.45)	0.40	46.47	0.17
Duration (weeks)					
>14	3	-0.27(-0.66, 0.11)	0.16	27.89	0.38
≤14	3	-0.41(-2.11, 1.30)	0.64	72.88	0.02
Age (years)					
>8	3	0.13(-2.18, 2.45)	0.91	65.53	0.08
≤8	3	-0.30(-0.55, -0.06)	0.02	0	0.80
Included articles					
>5	3	-0.04(-0.50, 0.41)	0.85	80.19	<0.001
≤5	3	-1.23(-3.39, 0.93)	0.27	23.45	0.39
Dosage (mg)					
>1000	4	-0.80(-1.93, 0.34)	0.17	37.47	0.27
≤1000	2	0.18(-0.16, 0.52)	0.29	47.80	0.17
Quality					
Critically low	2	-0.05(-0.80, 0.69)	0.89	91.13	<0.001
Low	4	-0.62(-2.06, 0.81)	0.40	52.50	0.13

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Irritability					
Overall	6	0.09(-0.12, 0.30)	0.42	0	0.89
Sample size (subjects)					
>110	4	0.09(-0.12, 0.30)	0.41	0	0.64
≤110	2	0.03(-1.82, 1.88)	0.98	0	0.87
Duration (weeks)					
>14	3	0.00(-0.27, 0.27)	0.98	0	0.72
≤14	3	0.23(-0.12, 0.57)	0.20	0	0.96
Age (years)					
>8	3	0.23(-0.12, 0.57)	0.20	0	0.96
≤8	3	0.00(-0.27, 0.27)	0.98	0	0.72
Included articles					
>5	3	0.09(-0.13, 0.30)	0.43	0	0.58
≤5	3	0.21(-1.57, 2.00)	0.81	0	0.74
Dosage (mg)					
>1000	4	0.02(-0.33, 0.38)	0.90	0	0.88
≤1000	2	0.12(-0.14, 0.39)	0.36	0	0.35
Quality					
Critically low	2	0.13(-0.12, 0.38)	0.32	0	0.40
Low	4	-0.01(-0.40, 0.38)	0.96	0	0.88
Social withdrawal/lethargy					
Overall	6	-0.22(-0.78, 0.35)	0.45	76.86	<0.001
Sample size (subjects)					
>110	4	-0.05(-0.50, 0.40)	0.83	72.94	0.01
≤110	2	-1.08(-3.61, 1.45)	0.40	46.47	0.17
Duration (weeks)					
>14	3	-0.27(-0.66,	0.16	27.89	0.38

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		0.11)			
≤14	3	-0.41(-2.11, 1.30)	0.64	72.88	0.02
Age (years)					
>8	3	-0.41(-2.11, 1.30)	0.64	72.88	0.02
≤8	3	-0.27(-0.66, 0.11)	0.16	27.89	0.38
Included articles					
>5	3	-0.04(-0.50, 0.41)	0.85	80.19	<0.001
≤5	3	-1.23(-3.39, 0.93)	0.27	23.45	0.39
Dosage (mg)					
>1000	4	-0.80(-1.93, 0.34)	0.17	37.47	0.27
≤1000	2	0.18(-0.16, 0.52)	0.29	47.80	0.17
Quality					
Critically low	2	-0.05(-0.80, 0.69)	0.89	91.13	<0.001
Low	4	-0.62(-2.06, 0.81)	0.40	52.50	0.13
Stereotypy/RRIB					
Overall	7	0.01(-0.29, 0.31)	0.95	64.30	0.01
Sample size (subjects)					
>110	5	0.05(-0.23, 0.33)	0.71	65.20	0.02
≤110	2	-0.22(-2.03, 1.59)	0.81	75.03	0.05
Duration (weeks)					
>14	4	-0.01(-0.38, 0.35)	0.94	65.82	0.02
≤14	3	-0.04(-0.98,	0.94	69.35	0.05

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		0.90)			
Age (years)					
>8	3	-0.04(-0.98, 0.90)	0.94	69.35	0.05
≤8	4	-0.01(-0.38, 0.35)	0.94	65.82	0.02
Included articles					
>5	3	-0.04(-0.41, 0.33)	0.85	73.64	0.02
≤5	4	0.09(-0.88, 1.07)	0.85	63.96	0.04
Dosage (mg)					
>1000	4	-0.24(-1.08, 0.60)	0.57	51.44	0.07
≤1000	3	0.19(0.03, 0.35)	0.02	0	0.58
Quality					
Critically low	2	-0.07(-0.69, 0.55)	0.82	87.17	0.01
Low	4	-0.03(-0.93, 0.88)	0.96	56.68	0.06
high	1	0.23(-0.01, 0.47)	0.06	-	-

Abbreviations: ESs: effect sizes; CI: confidence interval; RRIB: restricted and repetitive interests and behaviors

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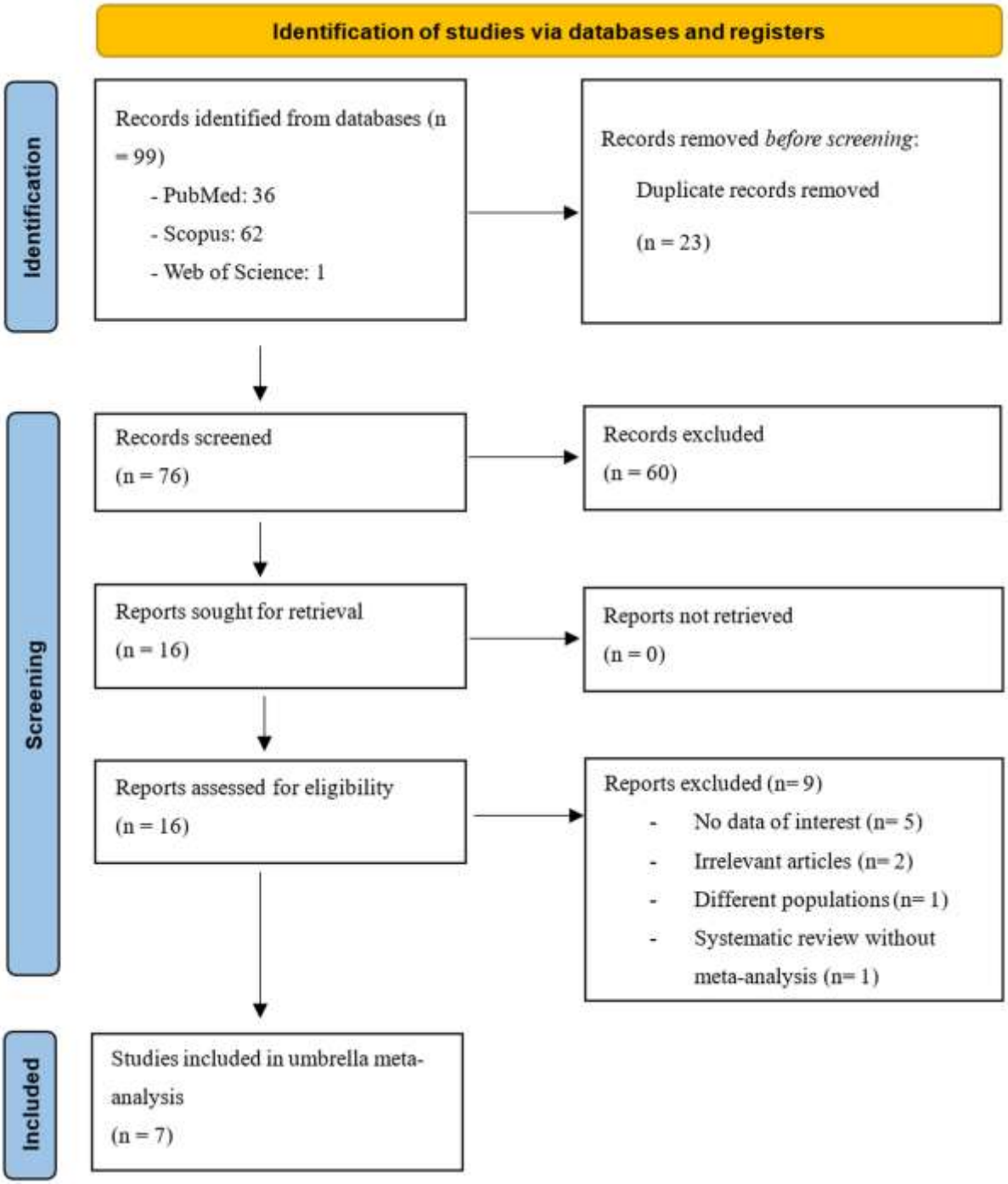

Figure 1. PRISMA flow chart of selected meta-analyses and systematic reviews

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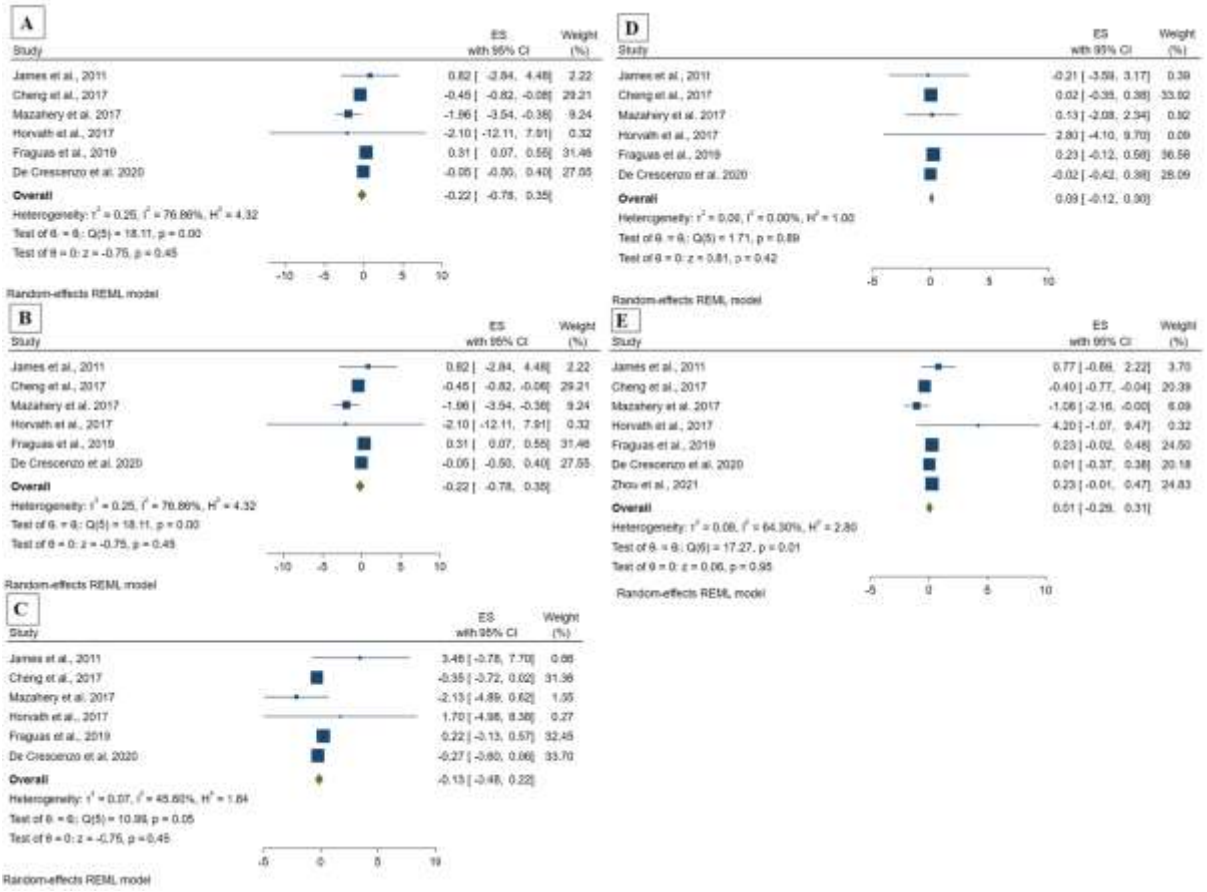

Figure 2. The forest plot of the effect of omega-3 fatty acid supplementation on social withdrawal/lethargy (A), cluttering speech (B), hyperactivity (C), irritability (D), and stereotypy/RRIB (E) in ASD patients utilizing ES with 95% CI.

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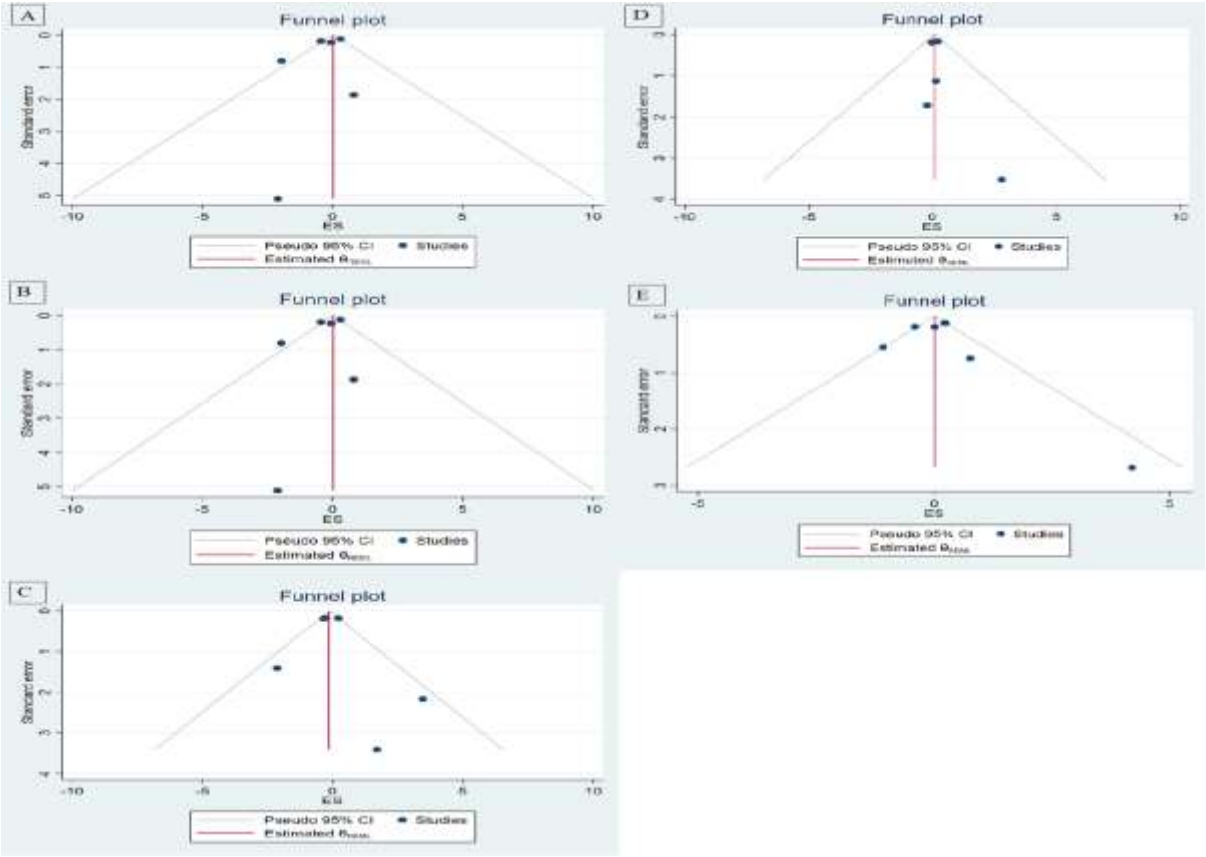

Figure 3. The funnel plot of the effect of omega-3 fatty acid supplementation on social withdrawal/lethargy (A), cluttering speech (B), hyperactivity (C), irritability (D), and stereotypy/RRIB (E) in ASD patients utilizing Trim-and-fill method.

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