Nutrition Research Reviews

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Impact of omega-3 fatty acid supplementation on clinical manifestations in autism spectrum disorders: an umbrella review of meta-analyses

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Review Article

Cite this article: Abbasi H, Parhiz A, Khoshdooz S, Bakhshimoghaddam F, Doaei S, and Gholamalizadeh M (2024). Impact of omega-3 fatty acid supplementation on clinical manifestations in autism spectrum disorders: an umbrella review of meta-analyses. *Nutrition Research Reviews*, page 1 of 12. doi: 10.1017/S0954422424000325

Received: 25 April 2024
Revised: 27 September 2024
Accepted: 12 November 2024

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

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition. Omega-3 fatty acid 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 the 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 up to December 2023. To assess the risk of bias, the assessment of multiple systematic reviews (AMSTAR)-2 was utilised. 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 acid supplementation caused a significant reduction in cluttering speech in studies conducted on age ≤8 years (effect size (ES) −0·30; 95% confidence interval (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 behaviours (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 with ASD who are 8 years old or younger.

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 behaviours (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 increased globally, with an estimated prevalence of 100 out of every 10 000 people in 2022[3]. Despite extensive investigation, the exact aetiology 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 has been 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-PUFA) 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-PUFA 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-PUFA[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, 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], whereas others found no significant effects[26,28,29]. Therefore, 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 utilising 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 (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])))). In addition, 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, studies with the following conditions were included: (1) systematic reviews and meta-analyses; (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 excluded from the analysis. The PICO of this umbrella review was as follows: Population/Patients (P: participants with ASD); Intervention (I: omega-3 fatty acid 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 utilised. This tool is designed to assess the quality of systematic reviews and has sixteen items with seven critical domains (containing items 2, 4, 7, 9, 11, 13 and 15) answering with ‘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 were 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 randomised controlled trials (RCT) were inserted in a predesigned Microsoft Word table.

Data synthesis and statistical analysis

For statistical analysis with effect sizes and confidence intervals, a random-effects restricted maximum likelihood model was utilised to execute this umbrella meta-analysis. Using the I^2 index, between-study heterogeneity was evaluated. Generally, an 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 and Tweedie ‘trim and fill’ analysis was performed. STATA version 16 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses, considering a significance level of $P < 0{\cdot}05$.

Results

Study selection

Meta-analyses of RCT with publication years ranging from 2011 to 2021 were included in the present study. As shown in Fig. 1, through the initial systematic searches, ninety-nine eligible articles were retrieved. After removing duplications, seventy-six records were screened in the title/abstract evaluation phase, of which sixty papers were excluded. Afterwards, based on the research topic, sixteen studies were obtained for assessing the full text, of which nine 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].

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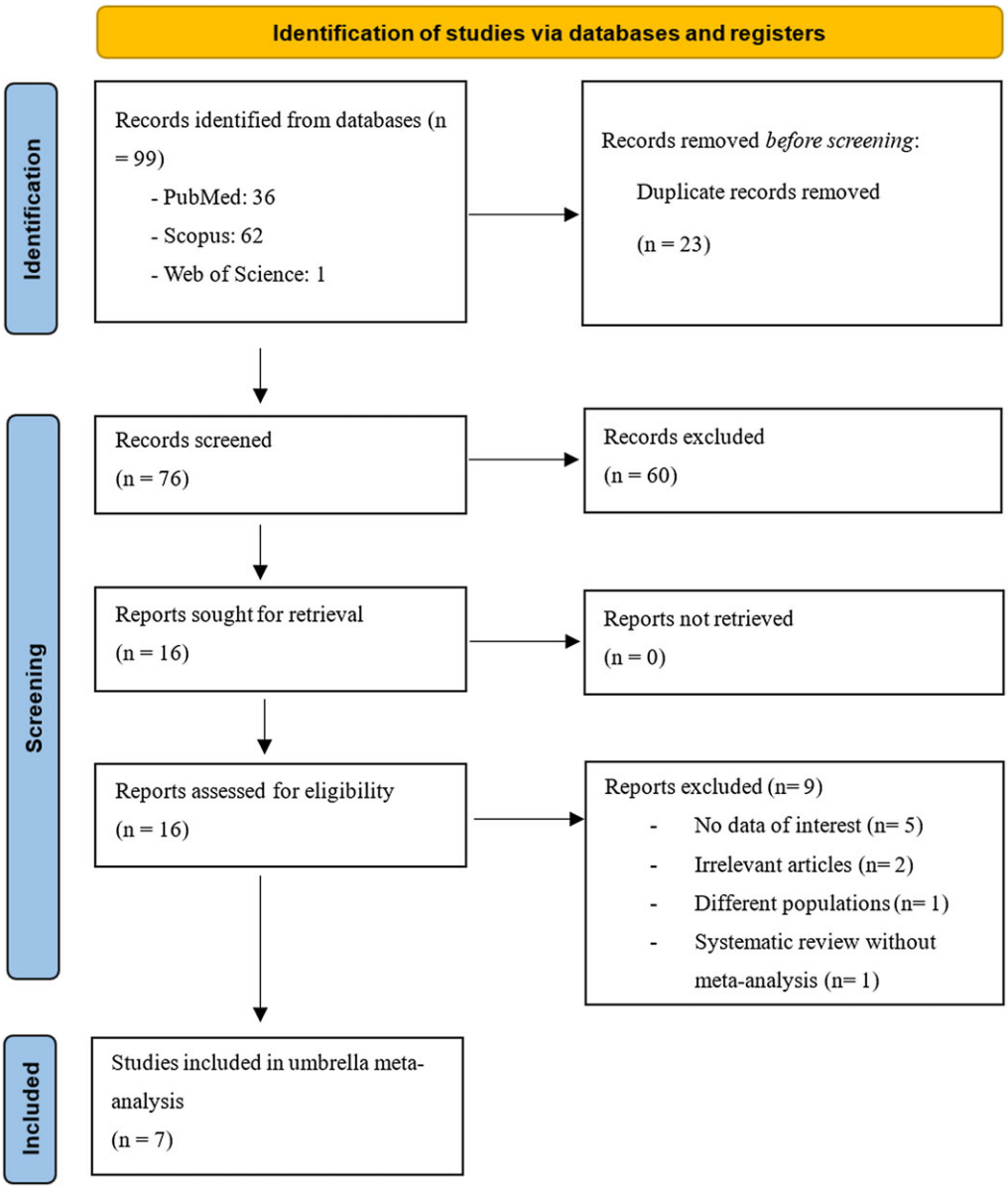

Figure 1. PRISMA flow chart of selected meta-analyses and systematic reviews.

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 seven meta-analyses selected, two studies were executed in the USA [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 the UK[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 behaviours (RRIB) ($n = 7$). In addition, some studies evaluated other outcomes, such as internalising, externalising, functional communication, adaptive skills, cognition, aggression, quality of sleep, self-harm or attention.

Results of methodological quality assessment

Based on the AMSTAR-2, the findings of the quality assessment are presented 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 participants with ASD (ES −0·22; 95% CI −0·78, 0·35; $P = 0·45$). However, a significant between-study heterogeneity was observed ($I^2 = 76·86\%$,

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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 (years)	Intervention (range and mean of dose and duration)	Omega 3 type	Quality assessment scale	Outcomes[(significance/non-significance)]
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 behaviours [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] • Internalising [NS] • Externalising [NS] • Functional communication [NS] • Social skills [NS] • Behavioural [NS] • Adaptive skills [NS] • 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 behaviours [NS]

Table 1. (*Continued*)

De Crescenzo *et al.* 2020[37]	9	UK 2007–2018	405	7·3	200–1500 mg/d (901·3 mg/d) 6–52 wks (18 wks)	EPA and DHA	1·4/4	• Hyperactivity ^{NS} • Aggression ^{NS} • Irritability ^{NS} • Anxiety $^{S\downarrow}$ • Adaptive functioning ^{NS} • Social interaction ^{NS} • Restricted and repetitive interests and behaviours ^{NS} • Communication ^{NS} • Quality of sleep ^{NS} • Self-harm ^{NS} • Attention ^{NS} • Hyperactivity and disruptive behaviours ^{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; down arrow, reductuin; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not available.

$P < 0{\cdot}001$). Evidence of a small-study effect was not observed (Egger's ($P = 0{\cdot}32$) and Begg's tests ($P = 1{\cdot}00$)). Publication bias analysis demonstrated that the shape of the 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; $P > 0{\cdot}05$).

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 Fig. 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; $P = 0{\cdot}45$), although there was a significant between-study heterogeneity ($I^2 = 76{\cdot}86\%$, $P < 0{\cdot}001$). Subgroup analysis according to age revealed that cluttering speech was significantly reduced in studies conducted on participants aged ≤8 years (ES −0·30; 95% CI −0·55, −0·06; $P = 0{\cdot}02$) (Table 3). The small-study effects were assessed by performing Egger's and Begg's tests ($P = 0{\cdot}32$ and 1·00, respectively). However, visual inspection of the 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; $P > 0{\cdot}05$).

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; $P > 0{\cdot}05$) (Fig. 2c), although a significant between-study heterogeneity was observed ($I^2 = 45{\cdot}60\%$, $P = 0{\cdot}05$). Subgroup analysis based on age and study duration showed significant reductions in hyperactivity in participants ≤8 years (ES = −0·30; 95% CI: −0·55, −0·06; $P = 0{\cdot}02$) and in participants who received omega-3 fatty acid supplementation for more than 14 weeks (ES −0·30; 95% CI −0·55, −0·06; $P = 0{\cdot}02$) (Table 3). Evidence of a small-study effect was not observed (Egger's test $P = 0{\cdot}61$ and Begg's tests $P = 1{\cdot}00$). Publication bias analysis demonstrated that the shape of the funnel plot was asymmetric (Fig. 3c). In accordance with this, the trim-and-fill analysis was performed with six studies and found no publication bias (ES −0·13; 95% CI −0·33, 0·07; $P > 0{\cdot}05$).

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; $P > 0{\cdot}05$) (Fig. 2d) with a low between-study heterogeneity ($I^2 = 0\%$, $P = 0{\cdot}89$). Regarding subgroup analysis, the result did not change. The Egger's ($P = 0{\cdot}73$) and Begg's ($P = 1{\cdot}00$) tests found that the overall ES did not change by the exclusion of any individual study. In addition, the asymmetric shape of the funnel plot confirmed the presence of publication bias (Fig. 3d). The trim-and-fill method found no publication bias (ES 0·09; 95% CI −0·12, 0·30; $P > 0{\cdot}05$).

https://doi.org/10.1017/S0954422424000325 Published online by Cambridge University Press

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

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?

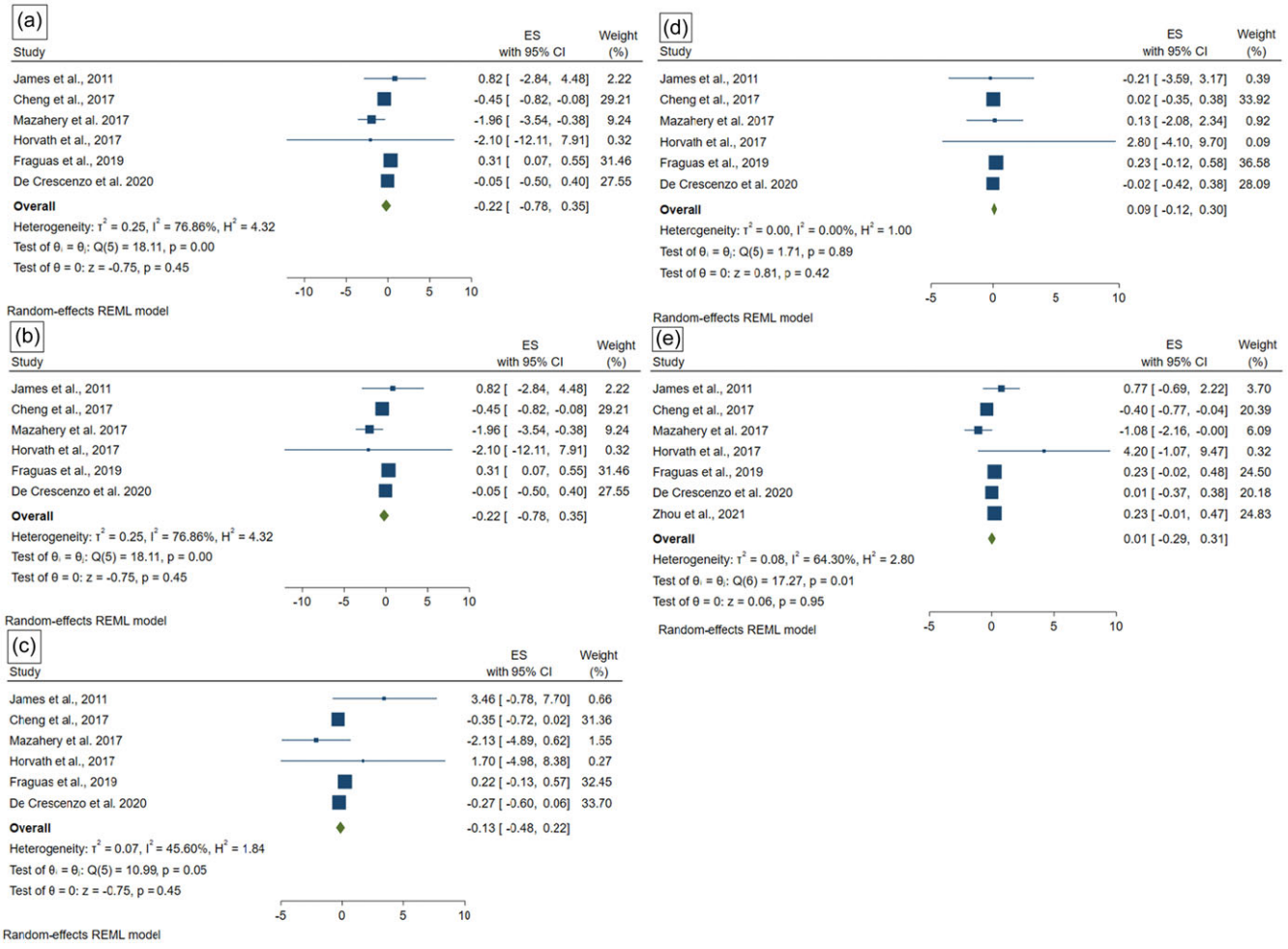

Figure 2. The forest plot of the effect of omega-3 fatty acid supplementation on social withdrawal/lethargy (a), cluttering speech (b), hyperactivity (c), irritability (d) and stereotypy/RRIB (e) in patients with ASD, presented as ES with 95% CI.

https://doi.org/10.1017/S0954422424000325 Published online by Cambridge University Press

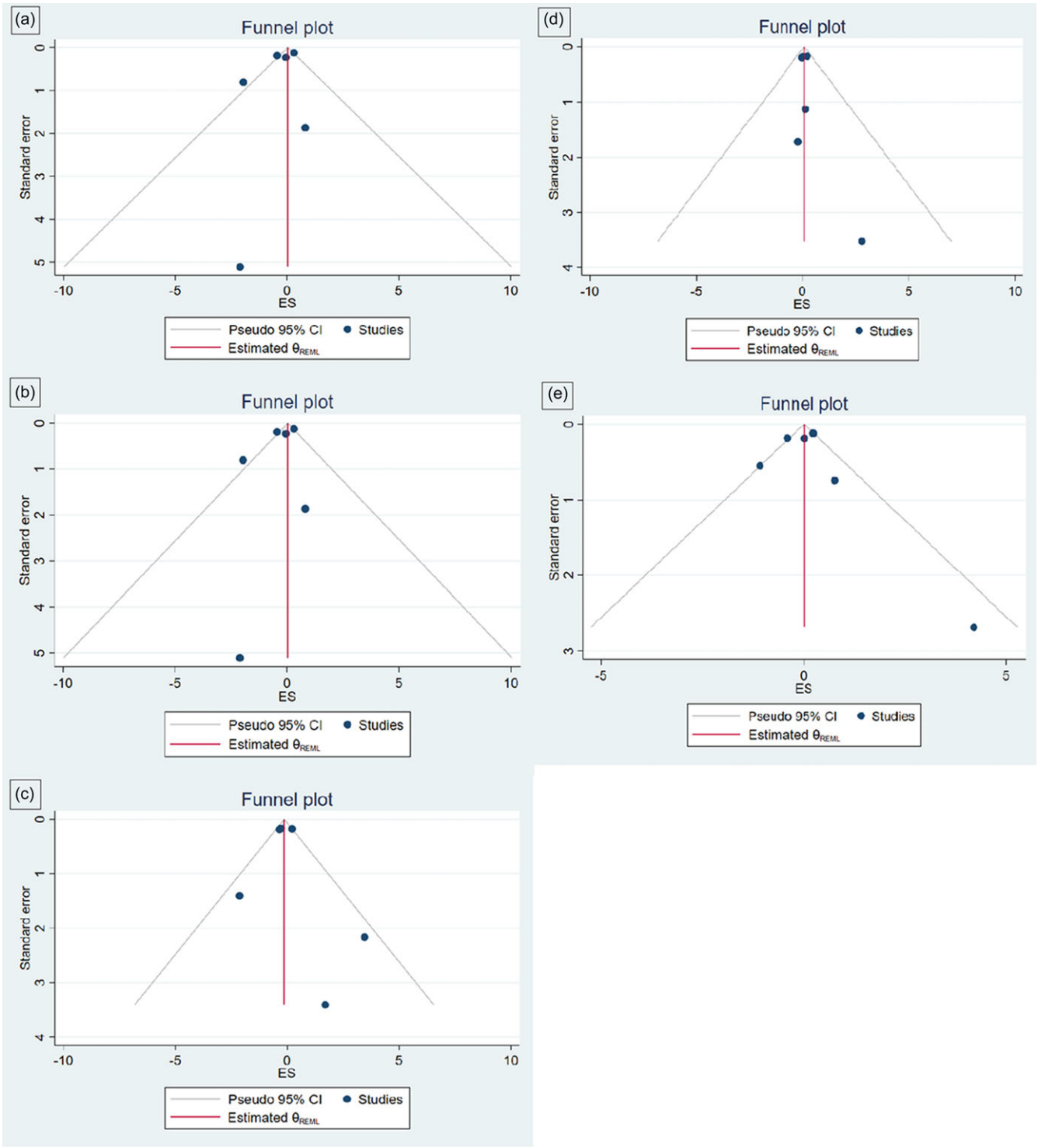

Figure 3. The funnel plot of the effect of omega-3 fatty acid supplementation on social withdrawal/lethargy (a), cluttering speech (b), hyperactivity (c), irritability (d) and stereotypy/RRIB (e) in patients with ASD, utilising the trim-and-fill method.

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

Based on seven 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 analysing subgroups on the basis of 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). A 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

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

Biochemical test	Effect size (number)	ES (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, 1·60)	0·90	40·54	0·17
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
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

(*Continued*)

https://doi.org/10.1017/S0954422424000325 Published online by Cambridge University Press

Table 3. (*Continued*)

Biochemical test	Effect size (number)	ES (95% CI)	*P* within	I^2 (%)	*P* heterogeneity
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, 0·11)	0·16	27·89	0·38
≤14	3	−0·41 (−2·11, 1·30)	0·64	72·88	0·02
Age (years)					
>8	3	−0·41 (−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, 0·90)	0·94	69·35	0·05

(*Continued*)

https://doi.org/10.1017/S0954422424000325 Published online by Cambridge University Press

Table 3. (*Continued*)

Biochemical test	Effect size (number)	ES (95% CI)	*P* within	I^2 (%)	*P* heterogeneity
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	–	–

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 a significant reduction in cluttering speech in studies conducted on participants aged ≤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 behaviour 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 externalising behaviours and a decline in social skills. In addition, a review examining various nutritional interventions, including omega-3 supplements, found that while many studies reported improvements in the behavioural symptoms of children with ASD, the wide variability in outcomes across these 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 RCT which reported no effect of omega-3 on the symptoms of ASD such as speech function[14]. However, 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 individuals with ASL 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 participants with ASD. 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 RCT which did not identify any benefits of omega-3 in reducing hyperactivity in participants with ASD [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 suggested 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 RCT 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 behaviour according to parental observations[35].

The results of the present study indicate 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]. Subgroup analysis of our research found that omega-3 supplementation with a dose of less than 1000 mg may increase the stereotypy or 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 types of fish was associated with higher Social Responsiveness Scale (SRS) scores

https://doi.org/10.1017/S0954422424000325 Published online by Cambridge University Press

(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 acid 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 randomised 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 been 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 subgroup analyses based on the severity of the disease and different types of fatty acid. 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 prioritise 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 standardise supplementation protocols and include diverse populations to enhance generalisability. 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 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 with ASD who are 8 years or younger. 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 acid are required to illuminate these particular aspects and to discover the underlying mechanisms of the effects of omega-3 fatty acids on ASD symptoms.

Data availability statement. All data generated or analysed during this study are included in this published article and its supplementary material.

Acknowledgements. None.

Author contributions. H.A.: systematic search; risk of bias assessment and preparing the figures; formal analysis, data interpretation, and writing-original draft; A.P: Conceptualisation and critically editing the manuscript; F.B., S.Kh.: study selection and data extraction; A.P., M.Gh.: conceptualisation and drafting the manuscript; S.D.: conceptualisation, supervision and critically editing the manuscript. All authors approved the final version for submission.

Competing interests. The authors declare no conflicts of interest.

Ethics approval. None.

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