



# The effect of omega-3 fatty acid supplementation on autism spectrum disorder: A meta-analysis

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## ARTICLE INFO

**Keywords:**

Omega-3 fatty acid

ASD

Meta-analysis

## ABSTRACT

**Background:** Omega-3 therapy for ASD is often used as a complementary and alternative medical approach, however, its impact on the core symptoms of ASD is controversial. Therefore, accurately determining the role of Omega-3 in ASD can establish a foundation for parents and doctors to formulate treatment plans. The current study aimed to include randomized controlled trials and provide a meta-analysis to evaluate the impact of Omega-3 fatty acids on the core symptoms of ASD.

**Method:** We searched the papers published in the Web of Science, PubMed, Medline, Scopus, EBSCO, SpringerLink, and Wiley Online Library databases until 10th April 2024 with 11 articles included. The meta-analysis evaluated the overall effects of Omega-3 fatty acids on core ASD behaviors and the effects on hyperactivity behavior, stereotype behavior, communication difficulty, and emotional difficulty.

**Results:** Results indicated that, compared to placebo, the Omega-3 fatty acids had a small and non-significant effect on the overall behavior [SMD= -0.1, 95 % CI (-0.36,0.17),  $p = 0.47$ ], with the same effect on hyperactivity behavior [SMD= -0.24, 95 % CI (-0.55,0.08),  $p = 0.14$ ], stereotyped behavior [SMD= -0.2, 95 % CI (-0.47,0.07),  $p = 0.15$ ], communication difficulty [SMD= -0.09, 95 % CI (-0.42,0.24),  $p = 0.60$ ], and emotional difficulty [SMD= -0.15, 95 % CI (-0.45,0.14),  $p = 0.3$ ].

**Conclusions:** Overall, Omega-3 fatty acids have a minor and insignificant effect on ASD behaviors, which may be related to treatment protocol and appropriateness of participants. In the future, more large-scale and rigorous randomized controlled trials are needed to further obtain more convincing conclusions.

## 1. Introduction

Autism spectrum disorder (ASD) is a pervasive developmental disorder that arises from neurological differences, characterized by social communication disorders and repetitive or restrictive behaviors (American Psychological Association, 2013). The latest data from Centers for Disease Control and Prevention (CDC) showed that 1 in 36 children in the USA is diagnosed with ASD (Maenner et al., 2023), representing a marked increase of nearly 22.2 % over the past 3 years (Maenner et al., 2021). The condition not only has a

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negative effect on physical and mental health for ASD individuals, but also imposes significant economic pressure on families and society (Rogge & Janssen, 2019). In light of the rapidly increasing prevalence and the serious impact, there is a pressing need to actively pursue early intervention strategies for ASD.

The etiology of ASD is still unclear and inconsistent, resulting in limited targeted treatment options (Masi et al., 2017). Medications approved for the treatment of impulsive irritability and challenging behavior in ASD, such as risperidone and aripiprazole, may include side effects such as drowsiness, fatigue, weight gain and vomiting (Anderson et al., 2007; Robb et al., 2011). Therefore, exploring available and safe intervention approaches is particularly important. In recent years, there has been considerable attention given to the use of complementary and alternative medicine (CAM) therapies for intervening in ASD. Studies indicated that in certain families, the usage rate of CAM has reached as high as 74 % (Brondino et al., 2015; Hanson et al., 2007), showcasing its potential applicability and efficacy as an intervention method. Among biological CAM therapies, nutritional interventions, such as specialized diets and vitamin supplements, stand out as the most common intervention approaches (Perrin et al., 2012). Due to its characteristic of naturalness, the nutritional therapy has been widely accepted by parents. Research showed that over 80 % of parents have attempted a specific type of nutritional intervention based on the symptoms and dietary needs of their ASD children (Lange et al., 2015). Unsaturated fatty acids, commonly used in nutritional supplements, are mainly classified into omega-3 and omega-6 series based on the position of double bonds. Previous studies have shown beneficial effects in improving certain core symptoms of ASD (Mazahery et al., 2020). However, with the shift in modern dietary patterns, the estimated ratio of omega-6 to omega-3 polyunsaturated fatty acids (PUFAs) has increased from the traditional 1:1 to approximately 16:1 in Western diets (Parletta et al., 2016). Since omega-6 and omega-3 fatty acids rely on the same set of enzymes for metabolism, excessive intake of omega-6 may impair the metabolism and utilization of omega-3. The imbalance may lead to inflammation and thrombosis (Simopoulos, 2002), thereby affecting neurological function (Sinn & Howe, 2008). Consequently, it is important to focus on the effects of omega-3 supplementation alone in improving ASD symptoms.

Omega-3 fatty acids are PUFAs composed of double bonds, with the furthest double bond from the carboxyl group located at the third carbon atom from the end (Chan & Cho, 2009). It mainly comprises three forms in human diet, namely ALA ( $\alpha$ -linolenic acid), DHA (docosahexaenoic acid), and EPA (eicosapentaenoic acid) (Chan & Cho, 2009). ALA is mainly present in vegetable oils, while DHA and EPA are predominantly found in seafood (Doughman et al., 2007). Due to the indispensable nature in the organism and the inability to be synthesized autonomously, omega-3 fatty acids are classified as essential fatty acids. Although ALA can be converted into DHA and EPA within the human body, the efficacy is remarkably limited, with only 5 %–10 % successfully transforming into EPA and 2 %–10 % converting to DHA (Anderson, 2009). Hence, dietary intake represents a crucial approach for supplementing omega-3 fatty acids. Research indicated that Omega-3 can effectively promote physical health (Nigam et al., 2018), and play a significant role in heart health (von Schacky et al., 2023), brain development (Innis, 2008), and anti-inflammatory response (Chen et al., 2018).

Previous randomized controlled trials (RCT) have demonstrated that children in the experimental group who consumed Omega-3 fatty acids exhibited significant enhancements in ASD symptoms, as evidenced by improvements in social communication (Mazahery et al., 2019; Parellada et al., 2017), reductions in stereotypical behaviors (Doaei et al., 2020), and alleviation of hyperactivity symptoms (Doaei et al., 2020; Lundbergh et al., 2022). However, there still exist other randomized, double-blind, and placebo-controlled trials indicated that there was no significant improvement in core symptoms among ASD children after intervention (Amminger et al., 2007; Bent et al., 2011; Johnson et al., 2010; Voigt et al., 2014). These contradictory findings may be attributed to the differences in participant characteristics, intervention supplements, and measurement methods. Recent systematic reviews and meta-analyses have shown that there is not sufficient evidence to determine whether omega-3 fatty acids are effective for ASD (Bent et al., 2009; de Andrade Wobido et al., 2022). It may be related to the absence of symptomatic subgroup analysis and sensitivity analysis, highlighting the need for further confirmation of the results.

Therefore, based on current research evidence, this study conducted a latest and rigorous meta-analysis of randomized controlled trials (RCT) to examine the impact of Omega-3 fatty acids on core symptoms in ASD individuals. Compared with previous meta-analysis, we categorized the typical symptoms of ASD into various research dimensions and placed greater emphasis on the improvement of specific performance under the influence of Omega-3. This approach aimed to provide a more precise depiction of the actual effectiveness, thereby laying a foundation for doctors and parents to determine more suitable potential treatment plans.

## 2. Methods

### 2.1. Search strategy and selection criteria

The current study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al., 2009). The study protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (Protocol ID: CRD42024534414). Two independent reviewers searched the Web of Science, PubMed, Medline, Scopus, EBSCO, SpringerLink, and Wiley Online Library databases for related studies published until April 10, 2024. Search items included ('autism' or 'autism spectrum disorder' or 'autistic' or 'ASD') and ('omega 3' or 'omega3' or 'omega-3' or 'polyunsaturated fatty acids' or 'polyunsaturated fatty acid'). An additional manual search was conducted by examining the reference lists of eligible studies, literature reviews, and meta-analyses to ensure comprehensive coverage.

All studies included in this meta-analysis followed the PICOS (population, intervention, comparison, outcome) strategy: (1) the study was conducted in ASD population groups; (2) the experimental group received intervention with omega-3 supplementation; (3) the comparison group received intervention with placebo; (4) the study evaluated at least one of the core symptoms of ASD. We excluded patents, commentaries, literature reviews, non-English articles, and animal studies. Two authors reviewed the full text to determine if it met the inclusion criteria, and the discrepancies were resolved through consensus.

## 2.2. Data extraction

We extracted the following information from the included articles: first author, publication year, country, characteristics of ASD individuals, dosage of omega-3, duration of experiment, changes of ASD symptoms, and outcome assessment tool. In response to the issue that some studies only reported the ASD symptoms data during the period of baseline and the final intervention, we used the Cochrane data conversion tool to transform the mean values and standard deviation (SD) values, thereby unifying the data results (Higgins et al., 2019). Data were independently collected by two authors using a standardized extraction form. When discrepancies appeared between the two authors during the data extraction process, a third author was consulted to determine the final result.

## 2.3. Study quality

The Cochrane risk of bias tool was used to evaluate the quality of included studies. The assessment tool is divided into five domains: random sequence generation (selection bias), allocation concealment (selective bias), blinding of participants and personnel (performance bias), incomplete outcome data (attribution bias), and selective reporting (reporting bias). The included articles were classified as low risk, unclear risk, and high risk, in accordance with the Cochrane manual (Higgins et al., 2011).

## 2.4. Data analysis

The current study was conducted using Stata 17 and Review Manager 5.4.1 software. The standard mean deviation (SMD) and 95 % confidence interval (CI) was used as statistical indicators to analyze the treatment efficacy. Initially, a statistical analysis was conducted on the primary scale results reported in each study. Furthermore, a subgroup analysis was undertaken, focusing on the core symptoms of ASD commonly reported on different scales in each study (hyperactivity behavior, stereotyped behavior, communication difficulty, and emotional difficulty). The mean and SD value of the changes in primary results and specific behavior score were obtained, with negative value indicating the improvement. Given the variations in scoring standards across different scales, the mean

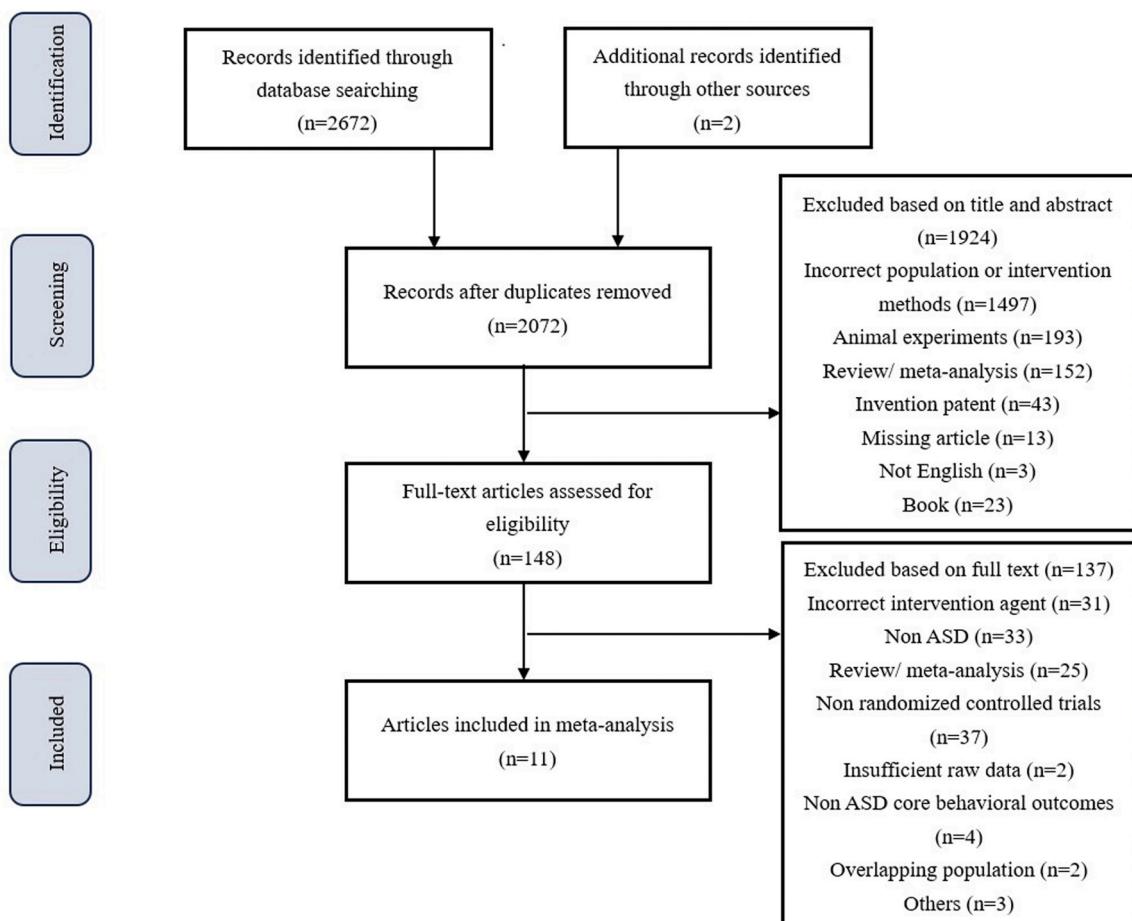
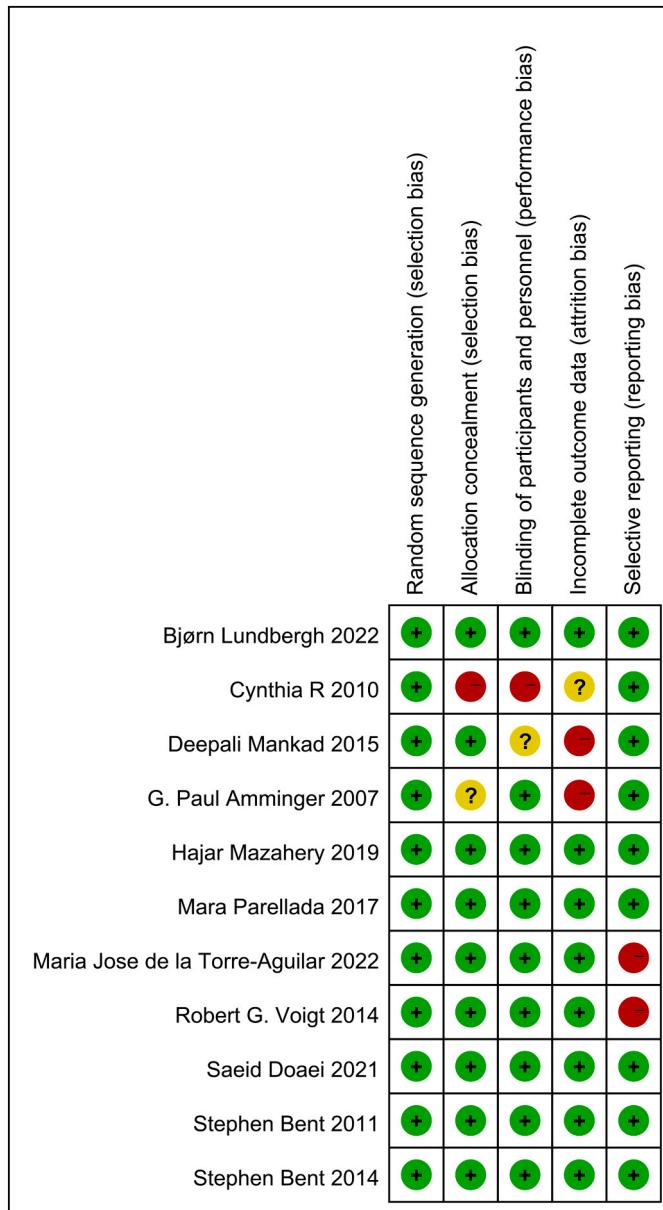


Fig. 1. Study flowchart.

values of outcomes measured in opposite directions were multiplied by negative one to ensure consistency of the results (Higgins, 2011). Due to the diversity of study populations and the differences in measurement tools, a random-effects model was utilized for estimation. The forest plot visually presented the meta-analysis results, including the weights of individual studies, 95 % CI, and the overall improvement effect of all studies. Meanwhile, Chi-square and  $I^2$  tests were conducted to assess statistical heterogeneity, with  $I^2$  values of 0 %, 25 %, 50 %, and 75 %, indicated no, low, moderated, and high heterogeneity between studies (Higgins et al., 2003). For all tests,  $p < 0.05$  was indicated statistically significant. Moreover, the funnel plots and Egger regression model was undertaken to assess the publication bias, while sensitivity analysis was conducted to estimate the stability of the results.

### 3. Results

The flowchart of the study selection process was illustrated in Fig. 1. In this meta-analysis, a total of 2672 papers were searched from the database, and two were obtained from the references of published literature reviews. Among them, 602 duplicates were removed, and 1924 articles that did not meet the inclusion criteria were excluded through screening of titles and abstracts. Full text screening was conducted on the remaining 148 articles, of which 11 met the criteria.



**Fig. 2.** Risk of bias summary.

### 3.1. Characteristics of the included studies

A total of 11 randomized controlled trials (RCT) were involved in the meta-analysis. As outlined in **Table 1**, these studies originated from seven different countries: USA (4), Spain (2), Austria (1), New Zealand (1), Canada (1), Denmark (1), and Iran (1), spanning a publication period from 2007 to 2022. A total of 416 ASD individuals were recruited, major of whom were children and adolescents, with ages averaging between 3 and 12 years old. Notably, the majority of participants were male, with a ratio of 4.17:1, which closely mirrored the widely acknowledged male-to-female ratio of 4:1 for ASD ([Autism and Developmental Disabilities Monitoring Network, 2012](#)). Regarding the RCT process, the dosage range of omega-3 intervention supplements was between 200 mg and 4000 mg, and the duration of intervention varied from 1 month to 12 months, reflecting differences in experimental settings. In terms of the outcome measurement, the tools used in each research were diverse, but all were related to measuring the core symptoms of ASD, such as social behavior, repetitive and stereotyped behavior.

### 3.2. Risk of bias in the included studies

The risk of bias summary and risk of bias graph were shown in [Fig. 2](#) and [Fig. 3](#). Regarding selection bias, all the included studies were randomly assigned to the experimental group and the control group, with 9 studies reporting allocation concealment schemes. In the process of intervention, 9 RCTs reported blinding of participants and personnel. In terms of results reporting, 3 studies presented missing data with high or unclear risks, of which 2 studies missed data related to the actual effects caused by omega-3 supplements, and 1 study did not provide clear explanations for the incomplete outcome. In addition, 2 studies failed to report all crucial data that were supposed to be illustrated, whereas the remaining studies provided data results that consistent with the pre-specified content. Overall, the quality of the eligible studies was generally satisfactory.

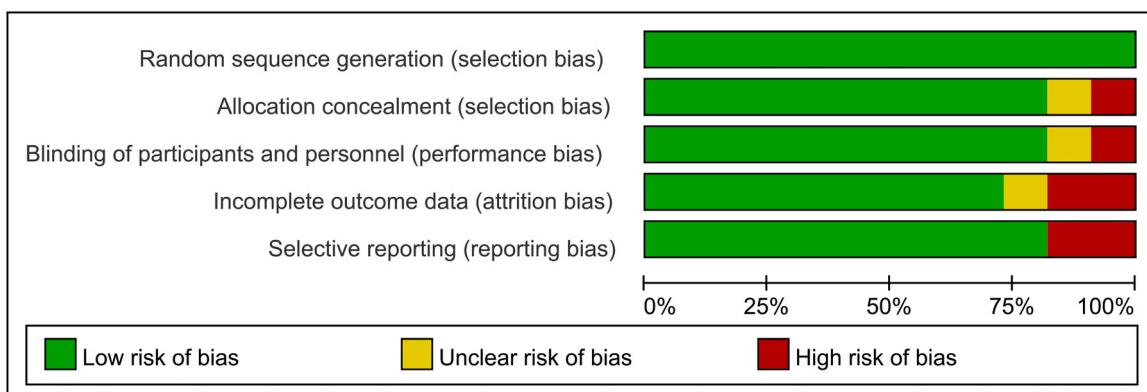
### 3.3. Outcome of meta-analysis

#### 3.3.1. The total effects of omega-3 on ASD

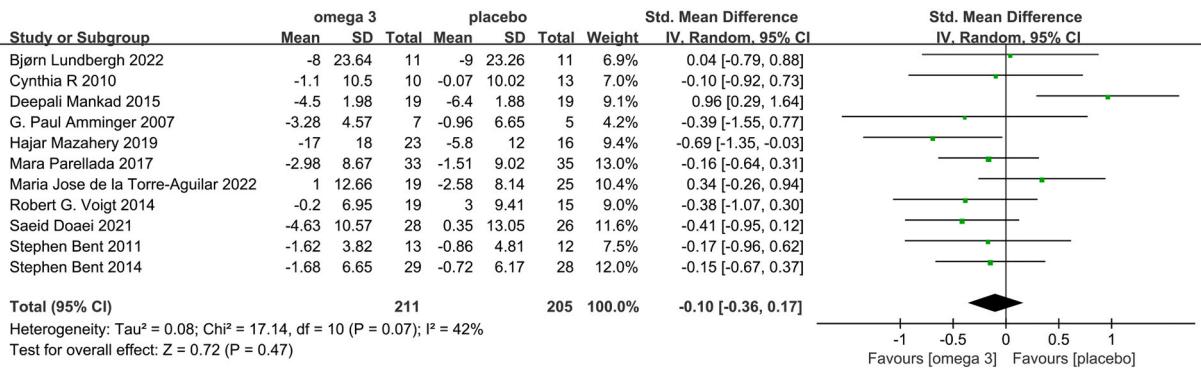
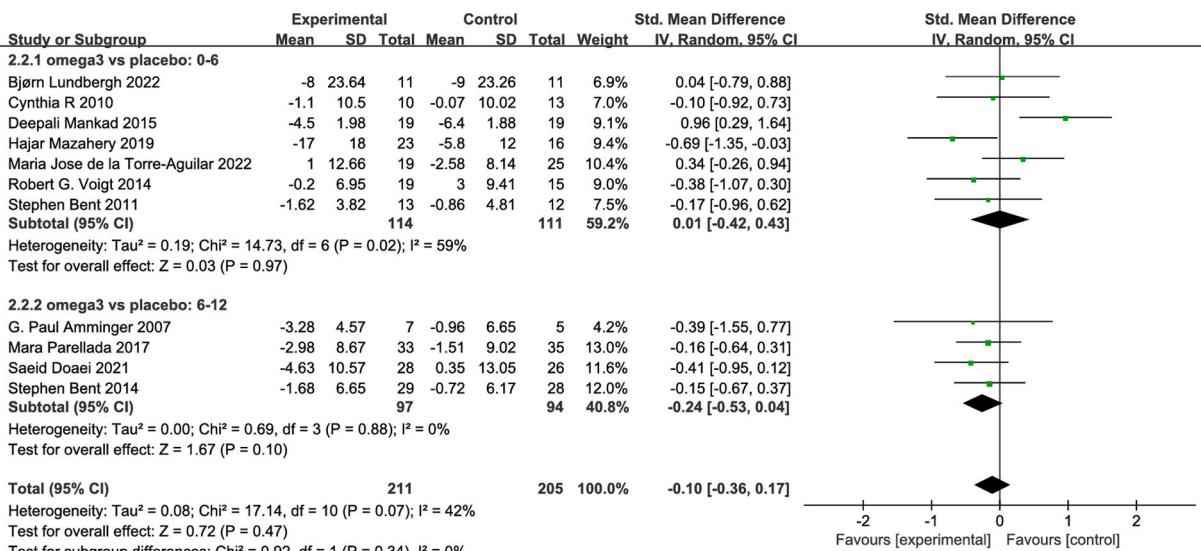
This meta-analysis encompassed a total of 416 ASD individuals, including 211 participants in the experimental group and 205 in the control group. [Fig. 4](#) depicted the effect of omega-3 supplementation on individuals with ASD. The analysis of 11 studies revealed low between-study heterogeneity, within an acceptable level ( $I^2=42\% < 50\%, p = 0.07$ ). The results indicated that, in comparison to placebo, the effect of omega-3 had a small and non-significant effect on the improvement of ASD symptoms [ $SMD = -0.1$ , 95 % CI  $(-0.36, 0.17)$ ,  $p = 0.47$ ]. In addition, this meta-analysis divided participants into two age groups—children less than 6 years old and those aged 6 years and older—to examine the effects of omega-3 supplementation across age. The results indicate that omega-3 fatty acids did not have a significant effect on children in either group ([Fig. 5](#)).

#### 3.3.2. The specific effects of omega-3 on ASD

Six common measurement dimensions were identified by analyzing the scales used to measure the core symptoms of ASD. [Fig. 6](#) illustrates the effect of omega-3 supplementation on each dimension. The results of the sample data suggested that Omega-3 fatty acids have a small and non-significant positive effect on hyperactivity behavior [ $SMD = -0.24$ , 95 % CI  $(-0.55, 0.08)$ ,  $p = 0.14$ ], stereotyped behavior [ $SMD = -0.2$ , 95 % CI  $(-0.47, 0.07)$ ,  $p = 0.15$ ], communication difficulty [ $SMD = -0.09$ , 95 % CI  $(-0.42, 0.24)$ ,  $p = 0.60$ ], and emotional difficulty [ $SMD = -0.15$ , 95 % CI  $(-0.45, 0.14)$ ,  $p = 0.31$ ]. The meta-analysis revealed a moderate between-study heterogeneity ( $I^2=54\% > 50\%, p = 0.04$ ) in social difficulty. Further sensitivity analysis was undertaken to identify the reasons for heterogeneity. By conducting sequential removal of each study, it was observed that Maria et al.'s study contributes to the heterogeneity ([de la Torre-Aguilar et al., 2022](#)). Following the exclusion of this study,  $I^2$  of the remaining studies decreased from 54% to 25%, falling within an acceptable range.



**Fig. 3.** Risk of bias graph.

**Fig. 4.** Forest plot of the effects of omega-3 supplementation in individuals with ASD.**Fig. 5.** Forest plot of the effects of omega-3 supplementation on individuals with ASD across different age groups.

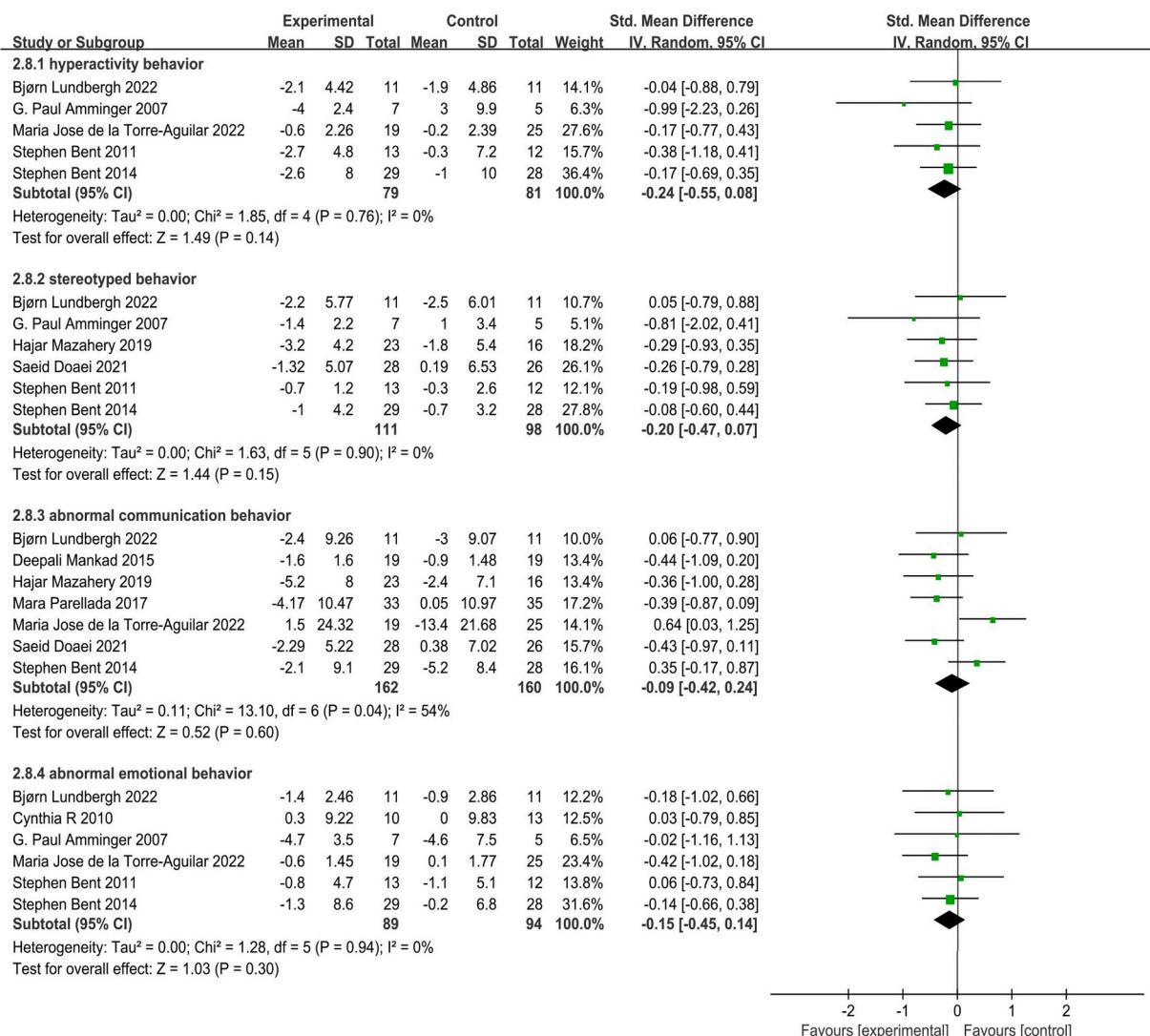
### 3.4. Publication bias assessment

Egger's test and funnel plot methods were employed to assess publication bias in the inclusion studies across four dimensions. The funnel plots in the meta-analyses exhibited symmetry (Fig. 7), and Egger's test indicated that the publication bias was not significant in hyperactivity behavior ( $p = 0.36$ ), stereotyped behavior ( $p = 0.54$ ), communication difficulty ( $p = 0.79$ ), and emotional difficulty ( $p = 0.60$ ).

### 4. Discussion

Omega-3 fatty acid serves as commonly used nutritional intervention method for ASD, but the efficacy is controversial. This meta-analysis included 11 studies, involving 416 individuals diagnosed with ASD, aiming to investigate the therapeutic impact of Omega-3 supplementation on ASD. Findings from our study indicated that the efficacy of Omega-3 is modest and non-significant for both overall and across sub-dimensions.

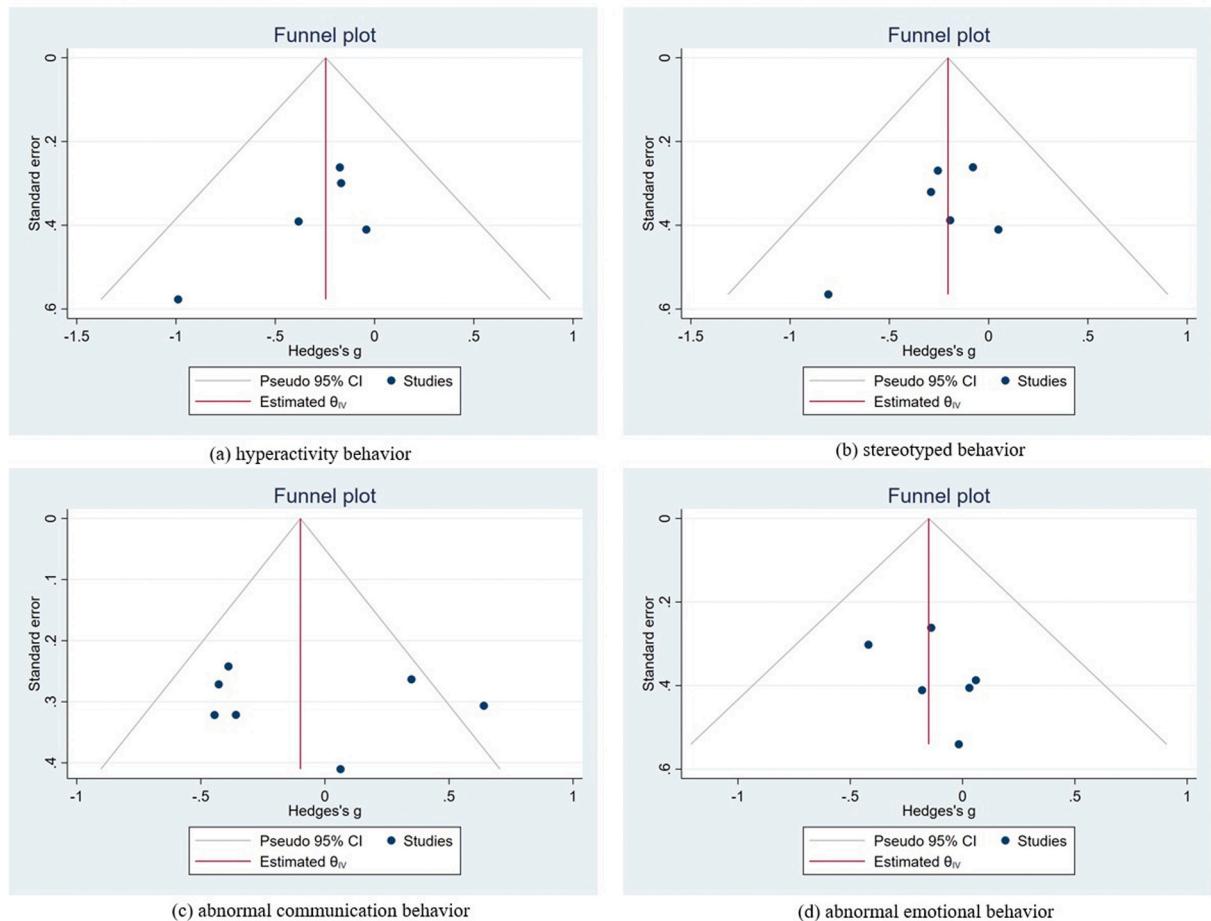
This study examined specific sub-dimensions, including hyperactivity behavior, stereotyped behavior, communication difficulty and emotional difficulty. Although some of these, such as hyperactivity and certain emotional responses, are not considered core features of ASD, such manifestations frequently occur as comorbid conditions. Therefore, it is also important to explore the potential benefits of omega-3 fatty acids in alleviating symptoms within specific sub-dimensions. Previous studies have revealed the efficacy of Omega-3 fatty acids in social communication (Mazahery et al., 2019; Parellada et al., 2017), stereotype behaviors (Doaei et al., 2020), and hyperactivity behaviors (Doaei et al., 2020; Lundbergh et al., 2022) in ASD individuals, our meta-analysis yielded unexpected findings, which can be explained in following aspects. First, the determination of ingredients, dosage, and duration of pharmacological intervention is vital for achieving precise and effective curative impacts (Rang, 2017). Among the included studies, the proportions of



**Fig. 6.** Forest plot of the effect of omega-3 supplementation on specific domains in individuals with ASD.

DHA and EPA in the intervention substances as well as the dosage and duration exhibited notable variations, potentially explaining the disparities in measurement outcomes. Second, although Omega-3 fatty acids have been shown to be associated with synaptic formation and neurite growth (Parellada et al., 2017), which might be the core of ASD neurophysiology, the efficacy has not been fully confirmed due to the complexity of the etiology. Numerous studies have demonstrated that supplementation with omega-3 fatty acids can improve the biological characteristics of ASD individuals, including the ratio of omega-3 fatty acids to total fatty acids in red blood cell membranes and the expression of IL-2 cytokines (Keim et al., 2022; Parellada et al., 2017; Yui et al., 2016). Nonetheless, there is a significant controversy regarding whether changes in the physiological markers can result in improvements in corresponding behavioral manifestations. Third, the effects of supplementing Omega-3 fatty acids on ASD individuals vary across different developmental stages (Karr et al., 2011). Research has shown that supplementing Omega-3 fatty acids in the first year of life has a positive effect on cognitive development in typically developmental children (Eilander et al., 2007). However, the influence become unclear as individuals grow (Eilander et al., 2007; Karr et al., 2011), which may be related to the fact that early life is a critical period for neurogenesis and plasticity (Johnson, 2001). Therefore, the age of participants included in the present study may also be one of the factors contributing to the slight effectiveness of the intervention.

Although our findings suggested that Omega-3 fatty acids have not shown significant improvement in ASD behavior for various reasons, in fact, it may be involved in the physiological regulation of ASD. The lower blood levels of Omega-3 PUFAs has been reported in ASD individuals (Agostoni et al., 2017), which may be related to the intake disorders caused by pickiness and the disruptions in the metabolism of fatty acids (de Andrade Wobido et al., 2022). Therefore, Omega-3 fatty acids are often recommended as nutritional supplements for individuals with ASD. Research has shown that nearly 900 genes are associated with ASD, and alteration in ASD-risk genes may affect the proteins encoded by these genes (Barón-Mendoza & González-Arenas, 2022; Carroll et al., 2020; SFARI, 2019). In



**Fig. 7.** Funnel plot of the effects of omega-3 supplementation on specific domains.

particular, these proteins are involved in intracellular signal transduction, cytoskeleton rearrangement, and neurite generation and elongation (Barón-Mendoza & González-Arenas, 2022). The underlying mechanism explains why differences in neuronal connections and synaptic plasticity have been widely regarded as a potential explanation for the etiology of ASD. Notably, Omega-3 fatty acids can modulate neuronal function by regulating membrane biophysics, releasing neurotransmitters, and promoting gene expression of synaptic proteins (Cao et al., 2009; Mostafa & Al-Ayadhi, 2015). Meanwhile, an alternative way for omega-3 to improve ASD symptoms is by regulating the composition of the gut microbiota, which refers to the community of microorganisms colonizing the digestive tract. These microorganisms affect the bidirectional signaling connections between the gastrointestinal tract and the brain by releasing chemicals (Mayer et al., 2014; Rhee et al., 2009). Studies suggested that individuals with ASD often possess a dysfunction in gut microbiota ecology, manifested by lower levels of bacterial genera, such as Bifidobacterium, Akkermansia, and Bacteroidota (Kittana et al., 2021; Luna et al., 2017). The supplementation of omega-3 fatty acids leads to a significant increase in the Bifidobacterium genus, and restores the Firmicutes/Bacteroidetes ratio (Costantini et al., 2017), which is beneficial for the synthesis of butyrate. Butyrate plays a crucial role in maintaining intestinal health, including anti-inflammatory effects, immune regulation, and the preservation of intestinal barrier integrity (Kittana et al., 2021; Nogay & Nahikian-Nelms, 2021). Meanwhile, Omega-3 fatty acids promote the attachment of probiotics to the intestinal wall and exert a synergistic effect with probiotics (Bifidobacterium and Akkermansia) (Das, 2003; El-Ansary & Bhat, 2020), which contributes to improve intestinal epithelial integrity and intestinal permeability (Veselinović et al., 2021). Therefore, the utilization of Omega-3 fatty acids as nutritional supplements for individuals with ASD is a physiologically grounded approach which required further investigation.

In the sensitivity analysis of this article, we found that the measurement tool used by Maria et al. in the social communication dimension is the source of heterogeneity (de la Torre-Aguilar et al., 2022). This is because the communication subscale items in this article focused on measuring receptive and expressive language (Mott, 1987), while the scales of other included studies focused on communication behavior characteristics. This implies that we should pay attention to the selection of measurement tools in the future. Additionally, it is crucial to clarify the specific intervention dosage, duration, material composition, and appropriate intervention age of participants, in order to further explore the intervention effect of Omega-3 fatty acids on ASD individuals.

## 5. Conclusion

In summary, our meta-analysis results indicated that compared to placebo, Omega-3 has a minor and insignificant impact on the overall and across-dimensions symptoms in ASD individuals. It may be influenced by various factors, including the treatment protocol and the appropriateness of the participants. Although the intervention of Omega-3 in ASD is grounded in physiological foundations, given the complexity of the ASD etiology, we should treat cautiously in assessing the role of Omega-3 in alleviating the core symptoms of ASD. In the future, more large-scale, rigorous, and precise randomized controlled trials should be conducted to acquire more convincing conclusions.

### CRediT authorship contribution statement

**Chang-Jiang Yang:** Writing – review & editing, Supervision, Funding acquisition. **Si-Jia Jia:** Writing – original draft, Data curation. **Li-Xin Yi:** Methodology, Conceptualization. **Jia-Qi Jing:** Writing – original draft, Methodology.

### Declaration of Competing Interest

All authors certify that they have no conflict of interest in this study to disclose.

### Acknowledgements

This research was supported by Shanghai Peak Project which was awarded to the corresponding author.

### Data availability

Data will be made available on request.

### References

- Agostoni, C., Nobile, M., Ciappolino, V., Delvecchio, G., Tesei, A., Turolo, S., Crippa, A., Mazzocchi, A., Altamura, C. A., & Brambilla, P. (2017). The role of omega-3 fatty acids in developmental psychopathology: A systematic review on early psychosis, autism, and ADHD. *International Journal of Molecular Sciences*, 18(12), 2608. (<https://www.mdpi.com/1422-0067/18/12/2608>).
- American Psychological Association. (2013). *Diagnostic and statistical manual of mental disorders*. DSM-5™, 5th ed.
- Amminger, G. P., Berger, G. E., Schäfer, M. R., Klier, C., Friedrich, M. H., & Feucht, M. (2007). Omega-3 fatty acids supplementation in children with autism: A double-blind randomized, placebo-controlled pilot study. *Biological Psychiatry*, 61(4), 551–553. (<https://doi.org/10.1016/j.biopsych.2006.05.007>)
- Anderson B.M., M.D.. (2009). *Are all n-3 polyunsaturated fatty acids created equal?*., 2009, 8. Available from: <https://doi.org/10.1186/1476-511X-8-33>. PMID: <https://www.ncbi.nlm.nih.gov/pubmed/19664246>, 33.
- Anderson, G. M., Scahill, L., McCracken, J. T., McDougle, C. J., Aman, M. G., Tierney, E., Arnold, L. E., Martin, A., Katsovich, L., Posey, D. J., Shah, B., & Vitiello, B. (2007). Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. *Biological Psychiatry*, 61(4), 545–550. (<https://doi.org/10.1016/j.biopsych.2006.02.032>)
- Autism and Developmental Disabilities Monitoring Network. (2012). Prevalence of autism spectrum disorders—Autism and developmental disabilities monitoring network, 14 sites, United States, 2008. In *Morbidity and mortality weekly report. surveillance summaries*, 61 pp. 1–19.
- Barón-Mendoza, I., & González-Arenas, A. (2022). Relationship between the effect of polyunsaturated fatty acids (PUFAs) on brain plasticity and the improvement on cognition and behavior in individuals with autism spectrum disorder. *Nutritional Neuroscience*, 25(2), 387–410. (<https://doi.org/10.1080/1028415X.2020.1755793>)
- Bent, S., Bertoglio, K., Ashwood, P., Bostrom, A., & Hendren, R. L. (2011). A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 41(5), 545–554. (<https://doi.org/10.1007/s10803-010-1078-8>)
- Bent, S., Bertoglio, K., & Hendren, R. L. (2009). Omega-3 fatty acids for autistic spectrum disorder: A systematic review. *Journal of Autism and Developmental Disorders*, 39(8), 1145–1154. (<https://doi.org/10.1007/s10803-009-0724-5>)
- Brondino, N., Fusar-Poli, L., Rocchetti, M., Provenzani, U., Barale, F., & Politi, P. (2015). Complementary and alternative therapies for autism spectrum disorder. *Evidence Based Complementary Alternative Medicine*, 2015, Article 258589. (<https://doi.org/10.1155/2015/258589>)
- Cao, D., Kevala, K., Kim, J., Moon, H.-S., Jun, S. B., Lovinger, D., & Kim, H.-Y. (2009). Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *Journal of Neurochemistry*, 111(2), 510–521. (<https://doi.org/10.1111/j.1471-4159.2009.06335.x>)
- Carroll, L., Braeutigam, S., Dawes, J. M., Krsnik, Z., Kostovic, I., Coutinho, E., Dewing, J. M., Horton, C. A., Gomez-Nicola, D., & Menassa, D. A. (2020). Autism spectrum disorders: Multiple routes to, and multiple consequences of, abnormal synaptic function and connectivity. *The Neuroscientist*, 27(1), 10–29. (<https://doi.org/10.1177/1073858420921378>)
- Chan, E. J., & Cho, L. (2009). What can we expect from omega-3 fatty acids? *Cleveland Clinic Journal of Medicine*, 76(4), 245–251. (<https://doi.org/10.3949/cjcm.76a.08042>)
- Chen, X., Chen, C., Fan, S., Wu, S., Yang, F., Fang, Z., Fu, H., & Li, Y. (2018). Omega-3 polyunsaturated fatty acid attenuates the inflammatory response by modulating microglia polarization through SIRT1-mediated deacetylation of the HMGB1/NF-κB pathway following experimental traumatic brain injury. *Journal of Neuroinflammation*, 15(1), 116. (<https://doi.org/10.1186/s12974-018-1151-3>)
- Costantini, L., Molinari, R., Farinon, B., & Merendino, N. (2017). Impact of omega-3 fatty acids on the gut microbiota. *International Journal of Molecular Sciences*, 18 (12), 2645. (<https://www.mdpi.com/1422-0067/18/12/2645>)
- Das, U. (2003). Long-chain polyunsaturated fatty acids in the growth and development of the brain and memory. *Nutrition*, 19(1), 62.
- de Andrade Wobido, K., de Sá Barreto da Cunha, M., Miranda, S. S., da Mota Santana, J., da Silva, D. C. G., & Pereira, M. (2022). Non-specific effect of omega-3 fatty acid supplementation on autistic spectrum disorder: systematic review and meta-analysis. *Nutritional Neuroscience*, 25(9), 1995–2007. (<https://doi.org/10.1080/1028415X.2021.1913950>)
- de la Torre-Aguilar, M. J., Gomez-Fernandez, A., Flores-Rojas, K., Martin-Borreguero, P., Mesa, M. D., Perez-Navero, J. L., Olivares, M., Gil, A., & Gil-Campos, M. (2022). Docosahexaenoic and Eicosapentaenoic intervention modifies plasma and erythrocyte omega-3 fatty acid profiles but not the clinical course of children with autism spectrum disorder: A randomized control trial [Clinical Trial]. *Frontiers in Nutrition*, 9. (<https://doi.org/10.3389/fnut.2022.790250>)

- Doaei, S., Bourbour, F., Teymoori, Z., Jafari, F., Kalantari, N., Torki, S., Ashoori, N., Gorgani, S., & Gholamalizadeh, M. (2020). The effect of omega-3 fatty acids supplementation on social and behavioral disorders of children with autism: a randomized clinical trial. *Pediatric Endocrinology Diabetes and Metabolism*, 27. <https://doi.org/10.5114/pedm.2020.101806>
- Doughman, S. D., Krupanidhi, S., & Sanjeevi, C. B. (2007). Omega-3 fatty acids for nutrition and medicine: Considering microalgae oil as a vegetarian source of EPA and DHA. *Current Diabetes Reviews*, 3(3), 198–203. <https://doi.org/10.2174/157339907781368968>
- Eilander, A., Hundscheid, D. C., Osendarp, S. J., Transler, C., & Zock, P. L. (2007). Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: A review of human studies. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 76(4), 189–203. <https://doi.org/10.1016/j.plefa.2007.01.003>
- El-Ansary, A., & Bhat, R. S. (2020). Chapter 17 - Targeting gut microbiota as a possible therapeutic intervention in autism. In U. Das, N. Papaneophytou, & T. El-Kour (Eds.), *Autism 360°* (pp. 301–327). Academic Press. <https://doi.org/10.1016/B978-0-12-818466-0.00017-4>
- Hanson, E., Kalish, L., Bunce, E., Curtis, C., McDaniel, S., Ware, J., & Petry, J. (2007). Use of complementary and alternative medicine among children diagnosed with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 37, 628–636. <https://doi.org/10.1007/s10803-006-0192-0>
- Higgins, J. (2011). *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration.
- Higgins, J. P., Altman, D. G., Gotzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343, d5928. <https://doi.org/10.1136/bmj.d5928>
- Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Bmj*, 327(7414), 557–560. <https://doi.org/10.1136/bmj.327.7414.557>
- Higgins JPT, T.J., Chandler J., Cumpston M., Li T., Page M.J., Welch V.A. (editors). (2019). *Cochrane handbook for systematic reviews of interventions*. 2nd Edition Chichester (UK): John Wiley & Sons.
- Innis, S. M. (2008). Dietary omega-3 fatty acids and the developing brain. *Brain Res*, 1237, 35–43. <https://doi.org/10.1016/j.brainres.2008.08.078>
- Johnson, C. R., Handen, B. L., Zimmer, M., & Sacco, K. (2010). Polyunsaturated fatty acid supplementation in young children with autism. *Journal of Developmental and Physical Disabilities*, 22(1), 1–10. <https://doi.org/10.1007/s10882-009-9152-x>
- Johnson, M. H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience*, 2(7), 475–483. <https://doi.org/10.1038/35081509>
- Karr, J. E., Alexander, J. E., & Winningham, R. G. (2011). Omega-3 polyunsaturated fatty acids and cognition throughout the lifespan: A review. *Nutritional Neuroscience*, 14(5), 216–225. <https://doi.org/10.1179/1476830511Y.00000000012>
- Keim, S. A., Jude, A., Smith, K., Khan, A. Q., Coury, D. L., Rausch, J., Udaipururia, S., Norris, M., Bartram, L. R., Narayanan, A. R., & Rogers, L. K. (2022). Randomized controlled trial of omega-3 + 6 fatty acid supplementation to reduce inflammatory markers in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 52(12), 5342–5355. <https://doi.org/10.1007/s10803-021-05396-9>
- Kittana, M., Ahmadani, A., Al Marzooq, F., & Attlee, A. (2021). Dietary fat effect on the gut microbiome, and its role in the modulation of gastrointestinal disorders in children with autism spectrum disorder. *Nutrients*, 13(11), 3818. (<https://www.mdpi.com/2072-6643/13/11/3818>).
- Lange, K. W., Hauser, J., & Reissmann, A. (2015). Gluten-free and casein-free diets in the therapy of autism. *Current Opinion in Clinical Nutrition and Metabolic Care*, 18 (6), 572–575. <https://doi.org/10.1097/mco.0000000000000228>
- Luna, R. A., Oezguen, N., Balderas, M., Venkatachalam, A., Runge, J. K., Versalovic, J., Veenstra-VanderWeele, J., Anderson, G. M., Savidge, T., & Williams, K. C. (2017). Distinct microbiome-neuroimmune signatures correlate with functional abdominal pain in children with autism spectrum disorder. *Cellular and Molecular Gastroenterology and Hepatology*, 3(2), 218–230. <https://doi.org/10.1016/j.jcmgh.2016.11.008>
- Lundbergh, B., Enevoldsen, A. S., Stark, K. D., Ritz, C., & Lauritzen, L. (2022). Fish oil supplementation may improve attention, working memory and attention-deficit/hyperactivity disorder symptoms in adults with autism spectrum disorder: A randomised crossover trial. *British Journal of Nutrition*, 1–11. <https://doi.org/10.1017/s0007114522000393>
- Maenner, M. J., Shaw, K. A., Bakian, A. V., Bilder, D. A., Durkin, M. S., Esler, A., Furnier, S. M., Hallas, L., Hall-Lande, J., Hudson, A., Hughes, M. M., Patrick, M., Pierce, K., Poynter, J. N., Salinas, A., Shenouda, J., Vehorn, A., Warren, Z., Constantino, J. N., DiRienzo, M., Fitzgerald, R. T., Grzybowski, A., Spivey, M. H., Pettygrove, S., Zahorodny, W., Ali, A., Andrews, J. G., Baroud, T., Gutierrez, J., Hewitt, A., Lee, L. C., Lopez, M., Mancilla, K. C., McArthur, D., Schwenk, Y. D., Washington, A., Williams, S., & Cogswell, M. E. (2021). Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2018. *MMWR Surveillance Summaries*, 70(11), 1–16. <https://doi.org/10.15585/mmwr.ss7011a1>
- Maenner, M. J., Warren, Z., Williams, A. R., Amoakohene, E., Bakian, A. V., Bilder, D. A., Durkin, M. S., FitzGerald, R. T., Furnier, S. M., Hughes, M. M., Ladd-Acosta, C. M., McArthur, D., Pas, E. T., Salinas, A., Vehorn, A., Williams, S., Esler, A., Grzybowski, A., Hall-Lande, J., Nguyen, R. H. N., Pierce, K., Zahorodny, W., Hudson, A., Hallas, L., Mancilla, K. C., Patrick, M., Shenouda, J., Sidwell, K., DiRienzo, M., Gutierrez, J., Spivey, M. H., Lopez, M., Pettygrove, S., Schwenk, Y. D., Washington, A., & Shaw, K. A. (2023). Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 Sites, United States, 2020. *MMWR Surveill Summ*, 72(2), 1–14. <https://doi.org/10.15585/mmwr.ss7202a1>
- Masi, A., DeMayo, M. M., Glozier, N., & Guastella, A. J. (2017). An overview of autism spectrum disorder, heterogeneity and treatment options. *Neuroscience Bulletin*, 33(2), 183–193. <https://doi.org/10.1007/s12264-017-0100-y>
- Mayer, E. A., Knight, R., Mazmanian, S. K., Cryan, J. F., & Tillisch, K. (2014). Gut microbes and the brain: Paradigm shift in neuroscience. *Journal of Neuroscience*, 34 (46), 15490–15496.
- Mazahery, H., Conlon, C. A., Beck, K. L., Mugridge, O., Kruger, M. C., Stonehouse, W., Camargo, C. A., Jr Meyer, B. J., Tsang, B., Jones, B., & von Hurst, P. R. (2019). A Randomised-controlled trial of vitamin D and omega-3 long chain polyunsaturated fatty acids in the treatment of core symptoms of autism spectrum disorder in children. *Journal of Autism and Developmental Disorders*, 49(5), 1778–1794. <https://doi.org/10.1007/s10803-018-3860-y>
- Mazahery, H., Conlon, C. A., Beck, K. L., Mugridge, O., Kruger, M. C., Stonehouse, W., Camargo, C. A., Jr Meyer, B. J., Tsang, B., & von Hurst, P. R. (2020). Inflammation (IL-1 $\beta$ ) modifies the effect of vitamin D and omega-3 long chain polyunsaturated fatty acids on core symptoms of autism spectrum disorder-an exploratory pilot study. *Nutrients*, 12(3). <https://doi.org/10.3390/nu12030661>
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The, P. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLOS Medicine*, 6(7), Article e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
- Mostafa, G. A., & Al-Ayadhi, L. Y. (2015). Reduced levels of plasma polyunsaturated fatty acids and serum carnitine in autistic children: Relation to gastrointestinal manifestations. *Behavioral and Brain Functions*, 11(1), 4. <https://doi.org/10.1186/s12993-014-0048-2>
- Mott, S. E. (1987). *Concurrent validity of the Battelle developmental inventory for speech and language disordered children*. *Psychology in the Schools*, 24(3), 215–220.
- Nigam, D., Yadav, R., & Tiwari, U. (2018). Omega-3 fatty acids and its role in human health. In In. V. Rani, & U. C. S. Yadav (Eds.), *Functional food and human health* (pp. 173–198). Springer Singapore. [https://doi.org/10.1007/978-981-13-1123-9\\_9](https://doi.org/10.1007/978-981-13-1123-9_9).
- Nogay, N. H., & Nahikian-Nelms, M. (2021). Can we reduce autism-related gastrointestinal and behavior problems by gut microbiota based dietary modulation? A review. *Nutritional Neuroscience*, 24(5), 327–338. <https://doi.org/10.1080/1028415X.2019.1630894>
- Parellada, M., Llorente, C., Calvo, R., Gutierrez, S., Lázaro, L., Graell, M., Guisasola, M., Dorado, M. L., Boada, L., Romo, J., Dulin, E., Sanz, I., Arango, C., & Moreno, C. (2017). Randomized trial of omega-3 for autism spectrum disorders: Effect on cell membrane composition and behavior. *European Neuropsychopharmacology*, 27 (12), 1319–1330. <https://doi.org/10.1016/j.euroneuro.2017.08.426>
- Parletta, N., Niyonsenga, T., & Duff, J. (2016). Omega-3 and omega-6 polyunsaturated fatty acid levels and correlations with symptoms in children with attention deficit hyperactivity disorder, autistic spectrum disorder and typically developing controls. *PLOS One*, 11(5), Article e0156432.
- Perrin, J. M., Coury, D. L., Hyman, S. L., Cole, L., Reynolds, A. M., & Clemons, T. (2012). Complementary and alternative medicine use in a large pediatric autism sample. *Pediatrics*, 130(2), S77–S82. <https://doi.org/10.1542/peds.2012-0900E>
- Rang, H. (2017). What is pharmacology? In In. R. Hill, T. Kenakin, & T. Blackburn (Eds.), *Pharmacology for chemists: Drug discovery in context* (p. 0). The Royal Society of Chemistry. <https://doi.org/10.1039/b9k781782621423-00001>.
- Rhee, S. H., Pothoulakis, C., & Mayer, E. A. (2009). Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nature Reviews Gastroenterology & Hepatology*, 6(5), 306–314. <https://doi.org/10.1038/nrgastro.2009.35>

- Robb, A. S., Andersson, C., Bellocchio, E. E., Manos, G., Rojas-Fernandez, C., Mathew, S., Marcus, R., Owen, R., & Mankoski, R. (2011). Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric subjects (6-17 years old): results from a pooled analysis of 2 studies. *Primary Care Companion for CNS Disorders*, 13(1). <https://doi.org/10.4088/PCC.10m01008gry>
- Rogge, N., & Janssen, J. (2019). The economic costs of autism spectrum disorder: A literature review. *Journal of Autism and Developmental Disorders*, 49(7), 2873–2900. <https://doi.org/10.1007/s10803-019-04014-z>
- SFARI. (2019). Gene Database. (Accessed 20 April 2024). Available from: <https://gene.sfari.org/>.
- Simopoulos, A. P. (2002). The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomedicine & Pharmacotherapy*, 56(8), 365–379.
- Sim, N., & Howe, P. (2008). Mental health benefits of omega-3 fatty acids may be mediated by improvements in cerebral vascular function. *Bioscience Hypotheses*, 1 (2), 103–108.
- Veselinović, A., Petrović, S., Žikić, V., Subotić, M., Jakovljević, V., Jeremić, N., & Vučić, V. (2021). Neuroinflammation in autism and supplementation based on omega-3 polyunsaturated fatty acids: A narrative review. *Medicina*, 57(9), 893. (<https://www.mdpi.com/1648-9144/57/9/893>).
- Voigt, R. G., Mellon, M. W., Katusic, S. K., Weaver, A. L., Matern, D., Mellon, B., Jensen, C. L., & Barbaresi, W. J. (2014). Dietary docosahexaenoic acid supplementation in children with autism. *Journal of Pediatric Gastroenterology and Nutrition*, 58(6), 715–722. <https://doi.org/10.1097/mpg.0000000000000260>
- von Schacky, C., Kuipers, R. S., Pijl, H., Muskiet, F. A. J., & Grobbee, D. E. (2023). Omega-3 fatty acids in heart disease—Why accurately measured levels matter. *Netherlands Heart Journal*, 31(11), 415–423. <https://doi.org/10.1007/s12471-023-01759-2>
- Yui, K., Imataka, G., Kawasak, Y., & Yamada, H. (2016). Increased ω-3 polyunsaturated fatty acid/arachidonic acid ratios and upregulation of signaling mediator in individuals with autism spectrum disorders. *Life Sciences*, 145, 205–212. <https://doi.org/10.1016/j.lfs.2015.12.039>