Supplementary materials

Table S1: PRISMA checklist of current meta-analysis

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8-9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12-15
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-15 table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-16, table 1
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	14-19, figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-19, figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	27

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table S2: Excluded studies and reasons

Meta-analysis (n=2)

James S, Montgomery P, Williams K. Omega-3 fatty acids supplementationfor autism spectrum disorders (ASD). Cochrane Database Syst Rev 2011;11:CD007992

Horvath A, Łukasik J, Szajewska H. ω-3 Fatty Acid Supplementation Does Not Affect Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis. J Nutr. 2017 Jan 11. pii: jn242354. doi: 10.3945/jn.116.242354. [Epub ahead of print]

Review articles (n=8)

Bent S, Bertoglio K, Hendren RL. Omega-3 fatty acids for autistic spectrum disorder: a systematic review. J Autism Dev Disord. 2009 Aug;39(8):1145-54. Epub 2009 Mar 31.

Tesei A, Crippa A, Ceccarelli SB, Mauri M, Molteni M, Agostoni C, Nobile M. The potential relevance of docosahexaenoic acid and eicosapentaenoic acid to the etiopathogenesis of childhood neuropsychiatric disorders. Eur Child Adolesc Psychiatry. 2016 Dec 17. doi: 10.1007/s00787-016-0932-4. [Epub ahead of print]

Bozzatello P, Brignolo E, De Grandi E, Bellino S. Supplementation with Omega-3 Fatty Acids in Psychiatric Disorders: A Review of Literature Data.J Clin Med. 2016 Jul 27;5(8). pii: E67. doi: 10.3390/jcm5080067.

van Elst K, Bruining H, Birtoli B, Terreaux C, Buitelaar JK, Kas MJ. Food for thought: dietary changes in essential fatty acid ratios and the increase in autism spectrum disorders. Neurosci Biobehav Rev. 2014 Sep;45:369-78. doi: 10.1016/j.neubiorev.2014.07.004.

Gumpricht E, Rockway S. Can ω-3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders? Nutrition. 2014 Jul-Aug;30(7-8):733-8. doi: 10.1016/j.nut.2013.11.001.

Williams K, Marraffa C. No evidence yet to support omega-3 fatty acids as a treatment for autism. J Paediatr Child Health. 2012 Jun;48(6):534-6.

Curtis LT, Patel K. Nutritional and environmental approaches to preventing and treating autism and attention deficit hyperactivity disorder (ADHD): a review. J Altern Complement Med. 2008 Jan-Feb;14(1):79-85. doi: 10.1089/acm.2007.0610.

Clayton EH, Hanstock TL, Garg ML, Hazell PL. Long chain omega-3 polyunsaturated fatty acids in the treatment of psychiatric illnesses in children and adolescents. Acta Neuropsychiatr. 2007 Apr;19(2):92-103. doi: 10.1111/j.1601-5215.2007.00189.x.

Discussion about study protocol, results not published yet (n=1)

Mazahery H , Conlon C , Beck KL , Kruger MC , Stonehouse W , Camargo CA , Meyer BJ , Tsang B , Mugridge O and vonHurst PR. Vitamin D and omega-3 fatty acid supplements in children with autism spectrum disorder : A study protocol for a factorial randomised, double-blind, placebo-controlled trial. Trials. 2016 Jun 23;17(1):295. doi: 10.1186/s13063-016-1428-8.

Not compared treatment effect of omega 3 (n=3)

Moreno C, Calvo-Escalona R, Gutierrez S, Graell M, Romo J, Dorado ML, Giraldez ML, Llorente C, Arango C, Parellada M. Effect of omega-3 polyunsaturated fatty acids on oxidative stress in children and adolescents with autism spectrum disorders. European neuropsychopharmacology, 2014, 24, S725

Meguid NA, Atta HM, Gouda AS, Khalil RO. Role of polyunsaturated fatty acids in the management of Egyptian children with autism. Clin Biochem. 2008 Sep;41(13):1044-8. doi: 10.1016/j.clinbiochem.2008.05.013.

Sliwinski S, Croonenberghs J, Christophe A, Deboutte D, Maes M. Polyunsaturated fatty acids: do they have a role in the pathophysiology of autism? Neuro Endocrinol Lett. 2006 Aug;27(4):465-71.

Not formally published study (n=1)

Parellada M, Llorente C, Calvo R, Gutierrez S, Lazaro L, Graell M, Alvarez M, Guisasola M, Dulin E, Dorado ML, Romo J, Arango C, Moreno C. Double-blind crossed-over randomized controlled-trial with omega-3 fatty acids for autism spectrum disorders. European neuropsychopharmacology, 2015, 25, S138

Animal studies (n=2)

Yadav S, Tiwari V, Singh M, Yadav RK, Roy S, Devi U, Gautam S, Rawat JK, Ansari MN, Saeedan AS, Prakash A, Saraf SA, Kaithwas G. Comparative efficacy of alpha-linolenic acid and gamma-linolenic acid to attenuate valproic acid-induced autism-like features. J Physiol Biochem. 2016 Nov 22.

Jašarević E, Hecht PM, Fritsche KL, Beversdorf DQ, Geary DC. Dissociable effects of dorsal and ventral hippocampal DHA content on spatial learning and anxiety-like behavior.Neurobiol Learn Mem. 2014 Dec;116:59-68. doi: 10.1016/j.nlm.2014.08.009.

Not RCT (n=7)

Ooi YP, Weng SJ, Jang LY, Low L, Seah J, Teo S, Ang RP, Lim CG, Liew A, Fung DS, Sung M. Omega-3 fatty acids in the management of autism spectrum disorders: findings from an open-label pilot study in Singapore. Eur J Clin Nutr. 2015 Aug;69(8):969-71. doi: 10.1038/ejcn.2015.28.

Al-Farsi YM, Waly MI, Deth RC, Al-Sharbati MM, Al-Shafaee M, Al-Farsi O, Al-Khaduri MM, Al-Adawi S, Hodgson NW, Gupta I, Ouhtit A. Impact of nutrition on serum levels of docosahexaenoic acid among Omani children with autism. Nutrition. 2013 Sep;29(9):1142-6. doi: 10.1016/j.nut.2013.03.009

Meiri G, Bichovsky Y, Belmaker RH. Omega 3 fatty acid treatment in autism. J Child Adolesc Psychopharmacol. 2009 Aug;19(4):449-51. doi: 10.1089/cap.2008.0123.

Politi P, Cena H, Comelli M, Marrone G, Allegri C, Emanuele E, Ucelli di Nemi S. Behavioral effects of omega-3 fatty acid supplementation in young adults with severe autism: an open label study. Arch Med Res. 2008 Oct;39(7):682-5. doi: 10.1016/j.arcmed.2008.06.005.

Schultz ST; Klonoff-Cohen HS; Wingard DL; Akshoomoff NA; Macera CA; Ji M; Bacher C. Breastfeeding, infant formula supplementation, and Autistic Disorder: the results of a parent survey. International Breastfeeding Journal. 1:16, 2006 Sep 15.

Al-Farsi YM; Waly MI; Deth RC; Al-Sharbati MM; Al-Shafaee M; Al-Farsi O; Al-Khaduri MM; Al-Adawi S; Hodgson NW; Gupta I; Ouhtit A. Impact of nutrition on serum levels of docosahexaenoic acid among Omani children with autism. Nutrition. 29(9):1142-6, 2013 Sep.

Johnson SM; Hollander E. Evidence that eicosapentaenoic acid is effective in treating autism. Journal of Clinical Psychiatry. 64(7):848-9, 2003 Jul.

Commentary articles (n=1)

Gilbert DL. Regarding "omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study". Biol Psychiatry. 2008 Jan 15;63(2):e13; author reply e15.

Duplicated sample sources: (n=2)

NCT00786799 had been published as Bent, S. (2011) [Bent S, Bertoglio K, Ashwood P, et al. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. J Autism Dev Disord 2011;41(5):545-54. doi: 10.1007/s10803-010-1078-8]

NCT01694667 had been published as Bent, S. (2014) [Bent S, Hendren RL, Zandi T, et al. Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. J Am Acad Child Adolesc Psychiatry 2014;53(6):658-66. doi: 10.1016/j.jaac.2014.01.018]

Not formal published and early terminated data: (n=1)

NCT01248130 did not provide definite outcome data available and this study was terminated early due to a change in the research priorities of the Principal Investigator in combination with low subject interest

Table S3: Jadad scores of recruited studies

Author (year)	Design	Country	Randomization	Blindness	Cohort	Total Jadad score
Mankad et al (2015)[1]	RCT	Canada	2	2	1	5
Bent et al (2014)[2]	RCT (Internet based)	USA	2	2	1	5
Voigt et al. (2014)[3]	RCT	USA	1	2	1	4
Yui et al (2012)[4]	RCT	Japan	2	2	1	5
Bent et al (2011)[5]	RCT	USA	2	2	1	5
Amminger et al (2007)[6]	RCT	Austria	1	2	1	4

Abbreviation: RCT: randomized controlled trials; USA: United States

References

1. Mankad D, Dupuis A, Smile S, et al. A randomized, placebo controlled trial of omega-3 fatty acids in the treatment of young children with autism. *Mol Autism*. 2015;6:18.
2. Bent S, Hendren RL, Zandi T, et al. Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. *J Am Acad Child Adolesc Psychiatry*. 2014;53(6):658–666.
3. Voigt RG, Mellon MW, Katusic SK, et al. Dietary docosahexaenoic acid supplementation in children with autism. *J Pediatr Gastroenterol Nutr*. 2014;58(6):715–722.
4. Yui K, Koshiba M, Nakamura S, Kobayashi Y. Effects of large doses of arachidonic acid added to docosahexaenoic acid on social impairment in individuals with autism spectrum disorders: a double-blind, placebo-controlled, randomized trial. J Clin Psychopharmacol. 2012;32(2):200–206.
5. Bent S, Bertoglio K, Ashwood P, Bostrom A, Hendren RL. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. J Autism Dev Disord. 2011;41(5):545–554.
6. Amminger GP, Berger GE, Schäfer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. Biol Psychiatry. 2007;61(4):551–553.