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Association of Omega 3 and Omega 6 and Child Development: A Systematic Review

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ABSTRACT

Introduction: Omega-3 and omega-6 long chain polyunsaturated fatty acids (LCPUFA) are the major components of structural central nervous system. This study aimed to summarize the relationship between omega-3 and/ or omega-6 LCPUFA on children development.

Method: Three large databases including Science Direct, Pubmed, and Cochrane were used to identify articles reporting the relationship of omega-3 and/or omega-6 and children development published between 2000 and 2021. The study was included if it was performed among under twelve children and provided the data of omega-3 and/ or omega-6 and cognitive development. This systematic review included both observational and experimental study. The publication bias was check using STROBE checklist.

Results: The result showed that 4 articles were included consisted of 3 observational studies and 1 experimental study. Two observational studies reported a significant association between omega-3 and/ or omega-6 and children development. However, the experimental study did not confirm these findings. Publications bias was observed in methodology, where the findings showed a weakness in generalizability.

Conclusion: This study concludes that omega-3 and omega-6 might play significant role in children development, but further study is needed to be done.

KEYWORDS

Omega-3, Omega-6, Child development, Systematic review.

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INTRODUCTION

Childhood development has been consistently described to directly affect child's future growth, well-being and even economic status[1–4]. Early nutritional status plays a critical role in shaping the development of children[5]. Better early childhood development is linearly associated with height for age and better body composition[6]. Moreover, certain polyunsaturated fatty acids (PUFA), including omega-3 and omega-6 fatty acids, has attracted considerable attention in childhood development[7]. Omega-3 and omega-6 refers the position of the first site of desaturation after the third and the sixth carbon from the carboxylic group, respectively[8]. Arachidonic acid (AA) and docosahexanoic acid (DHA) are the major of omega-3 and omega-6 fatty acids which are rapidly incorporated in the nervous system that possibly may affect the development[7,9].

Omega-3 and omega-6 fattys acid are main components of overall human membrane cells, including neuronal cells[10]. Previous studies reported that the augmentation intake of omega-3 and omge-6 were associated with the increase of neurogenesis[11]. Some other mechanisms may underline the effect of both fatty acids on brain function through the modifications of the fluidity of neuronal membrane, affinity of receptors, precursor of signaling molecules, enzymes activity, ion channel permeability, and neurotransmitter production[12]. Indeed, a systematic review suggests that omega-3 might be effective to reduce bipolar symptom[13]. However, both fatty acids have contrary effect in the formation of inflammatory lipids, thus the ratio balance is remarkably essential[14].

The contrary effect of omega-3 and omeg-6 may exhibit inconsistent results on cognitive development. The dietary intake of both fatty acids may compete each other for incorporation into cell membrane[15]. Animal studies showed that maternal diet high in omega-6 increased level of anxi-

ety of offspring, impaired neurogenesis and caused irreversible changes in hypothalamic composition[16–18]. Moreover, maternal concentrations of omega-6 were reported to have negatively associated with early behavior and development of premature infants, whereas omega-3 showed positive outcomes[19]. In addition, a case-control study found that children with epilepsy had higher levels of omega-6 but lower levels of omega-3 compared to non-epileptic children, which is suggested to impair cognitive function in those children[20]. Therefore, this study aimed to summarize the association between omega-3 and/ or omega-6 and child development through a systematic review. To the best of our knowledge, this is the first systematic review that has been performed.

METHODS

Search Strategy

A structured search was carried out to summarize the association between omega-3 and/or omega-6 fatty acids and children development. Three main scientific databases, including Science Direct, Pubmed, and Cochrane, were used to search the article published between 2000 and 2021. To obtain the relevant articles, the structured search used medical subheadings (MeSH) and other keywords including, "omega-3" OR "omega-6" AND "child development" OR "omega-3" AND "omega-6" AND "child development". The search was done in August 2021 and followed the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram[21]. Articles were included if met the following criteria: 1) study was performed among children aged under 12 years; 2) study provided the data of omega-3 and/ or omega-6 and cognitive development; 3) article was published in full-article and written in English. In addition, we collected the study either with observational or experimental design.

Study Selection and Data Extraction

The obtained articles were downloaded into Mendeley Web-Based Bibliographic Management Software. Study selection and data extraction were independently performed by two investigators. From the initial results, duplicates were removed, and the title and abstract were screened. Articles that were not original research or not evaluating the association of omega-3 and/ or omega-6 and child development were excluded.

Quality of Reporting and Risk of Bias Assessment

The quality of article was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement following the guidelines of the Enhancing the Quality and Transparency Of health Research (EQUATOR) framework. The statement was used as a checklist to rate the quality of reporting in the included papers[22,23]. This STROBE checklist consists of 22 statements that should represent in each included article. The checklist was then used to see the potential risk of publication bias.

RESULTS

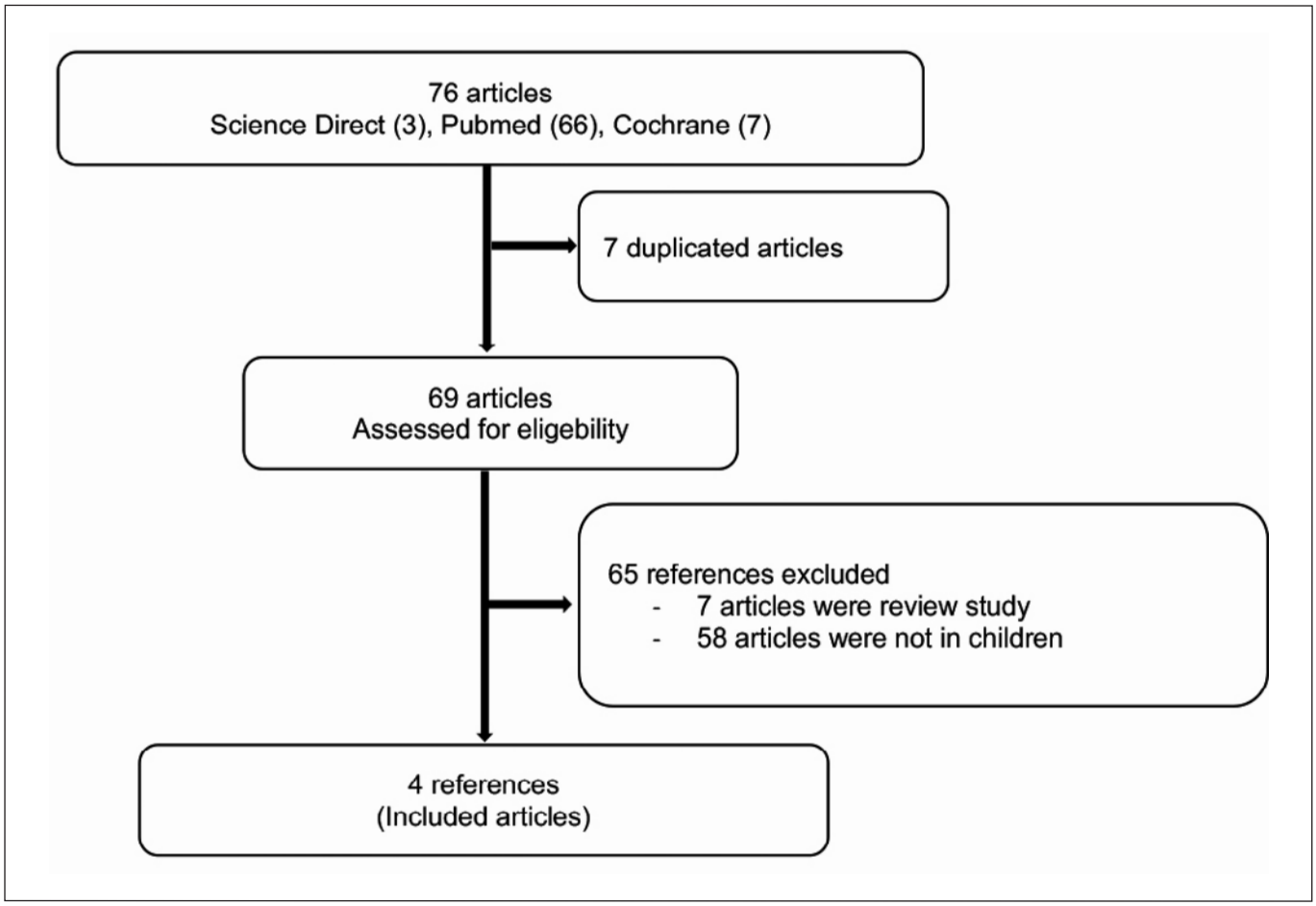
Results of the Literature Search and Study Characteristics

Literature search obtained 76 articles, including 66 articles from Pubmed, 33 articles from Science Direct, and 7 articles from Cochrane Database. From 76 articles, 7 articles were removed due to duplication. A total of 69 articles were in-depth screened for eligibility by reading the title and abstract. Furthermore, 65 articles were excluded, 7 articles were review study and 58 articles did not examine the cognitive development in children. Therefore, 4 articles were included in the present systematic review study. The flow diagram of literature identification can be seen in Figure 1.

The included articles were both from observational (3 articles) and experimental studies (1 article). Two articles were cohort study respectively conducted in UK (n = 6249) and USA (n = 183), and 1 article was a case-control study conducted in Japan (n case = 30, n control = 30). Moreover, a double-blinded, parallel group, randomized-controlled trial was conducted in India to investigate the effectiveness of DHA supplementation during pregnancy and 6 months postpartum on development quotient of 12 months infants. Only some of the developmental conditions in children were described, including social interaction in autism spectrum disorder (ASD) children, intelligence quotient (IQ), development quotient (DQ) and Mullen scales of early learnings (MSEL).

A significant association between omega-3 and/ or omega-6 with children development was only found in observational study. Usui et al.[24] reported a significant correlation between EPA, DHA, and AA plasma concentrations of children with social interaction score, indicating higher the plasma concentrations, more severe ASD syndrome. This showed the disruption of lipid metabolism in children with cognitive impairment. Steer et al. and Keim et al.[25,26] supported these findings, where they found that low levels of omega-3 and/ or omega-6 was associated with sub-optimal development. After 8 years following up, Steer et al.[25] demonstrated that low levels of AA and DH were associated with lower IQ performance, and full-scale IQ score, respectively. However, a cohort study which conducted by Keim et al.[26] found no significant association between breastmilk AA and DHA concentrations and children development aged 4 months which measured by MSEL. Also, the only experimental study on pregnant women consuming DHA supplementation (400 mg/d) from ≤20 weeks gestation to 6 months postpartum showed no significant difference in DQ scores of 12 months

Figure 1. Flow diagram of search strategy



infants compared to placebo group. The characteristics of included studies can be seen in Table 1.

Quality of Reporting Assessment

The results of STROBE checklist showed that the included studies mostly had weakness in methodological terms. The studies mainly did not provide information regarding the specific location, and relevant dates. Therefore, this may indicate high risk of bias particularly in generalizability. However, it should be noted that the included studies were from various study designs which might a different set of variables. The representation of the quality of the studies can be seen in Figure 2.

DISCUSSION

It has been widely suggested that omega-3 and omega-6 participate in the neurodevelopment of children[27]. This systematic review found that omega-3 and/ or omega-6 might have significant association with children cognitive development in observational studies. This is supported by the evidence that high consumption of omega-3 and omega-6 rich foods, including fish and seafoods, is associated with positive on IQ among school age children[28,29]. In addition, supplementation of fish oil in children showed benefit effect on problem solving and communicative development[30,31]. However, these findings could not be supported by the experimental study.

Omega-3 and omega-6 may play an important role in cognitive development through several mechanisms. Besides being the major structural components of central nervous system, these fatty acids also participate in enzymes activity, signaling, and antioxidant activity related to brain function[7]. DHA mediates the formation of neuroprotectin D1 (DPD1) which functions to down-regulate oxidative stress and brain cells apoptosis[32]. DHA also participates in brain glucose uptake by affecting the expression of glucose transporter, thus maintaining cognition function[33]. Also, AA is a retrograde messenger that enhances the production of neurotransmitter by presynaptic neuron[34]. In addition, an experimental study using mice with delat-6-desaturase knockout showed AA play a significant role in brain and overall development through growth hormone signaling pathway[35].

Table 1. Characteristic of Included studies

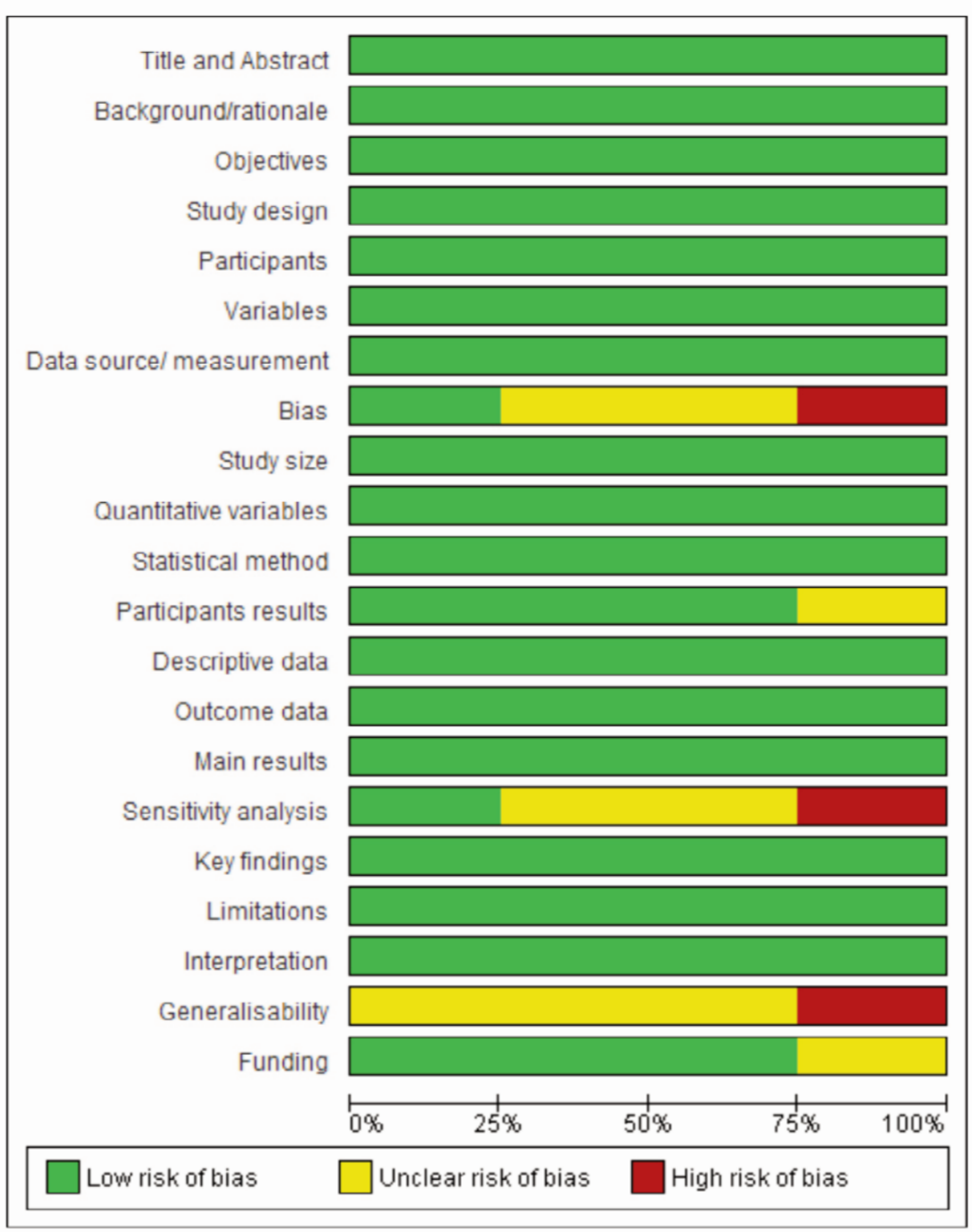
Author	Location	Study design	Participants	Fatty acids	Child development parameter	Result
Usui et al. (2020)	Japan	Case-control	Case: Children with ASD aged 5-11 years (n = 30) Control: Children with typical development aged 6-10 years (n = 30)	EPA, DHA, AA	Social interaction score (A score)	A score was significantly correlated with plasma concentration of EPA (r = 0.5706, P = 0.0069), DHA (r = 0.4880, P = 0.0248), and AA (r = 0.51292, P = 0.0159) by spearman rank correlation. This suggests that omega-3 and omega-6 plasma concentrations significantly increases in ASD, indicating the abnormalities of lipid metabolism in ASD.
Steer et al. (2013)	United Kingdom	Cohort	Children aged 8 years after following-up for 8 years (n = 6249)	AA and DHA	Child intelligence quotient (IQ)	Low levels of AA were associated with lower performance IQ (-2.0 points; 95% CI: -3.5. -0.6 points; P = 0.007). Also, low levels of DHA were associated with low level of full-scale IQ (-1.5 points, 95% CI: -2.91.-0.14); P = 0.031)
Keim et al. (2011)	United State of America	Cohort	Mothers were followed-up and infants' development at 12 months of age were assessed (n = 183)	Breast milk AA and DHA concentrations at 4 months post-partum were collected	Mullen Scales of Early Learnings (MSEL)	Both breastmilk AA and DHA concentrations were not significantly correlated with MSEL score (p > 0.05).
Khandelwal et al. (2020)	India	Double-blinded, parallel group, randomized, placebo controlled trial	957 pregnant women aged 18-35 years (n control = 479; n intervention = 478)	Supplementation of DHA (400 mg/d) from ≤20 weeks gestation to 6 months postpartum	Development quotient (DQ)	DQ scores of 12 months infants in the intervention and placebo groups were not statistically significant (96.6 ± 12.2 vs. 97.1 ± 13.0, p = 0.60)

EPA: eicosapentaenoic acid; DHA: docosahexaenoic Acid: AA: arachidonic acid; CI: confidence interval.

Unfortunately, our systematic review did not find the consistent results between the included studies, especially in experimental studies. This is in line with the previous studies demonstrated no beneficial effect of formula supplemented AA and DHA on the weight, length, visual acuity, and head circumference of infants[36–38]. Several explanations include, inadequate doses, number of days for intervention, and potentially socioenvironmental factors[39]. In addition, the effect may be observed after the first year, where the past study mainly measured the outcomes at the first year[36]. Moreover, it should be noted that since omega-3 and omega-6 have contrary activity, where ratio of omega-3/omega-6 is greatly enhanced by DHA but decreased by AA. Decrease in this ratio might increase the risk of ADHD. Thus, the balance combination of AA and DHA rather than AA or DH alone is suggested to be necessary for optimal brain development[35].

This study is the first systematic review to provide the integrated evidence of omega-3 and/ or omega-6 long chain polyunsaturated fatty acids (LC-PUFA) effect on children development. We explicitly reported the risk of bias for all included studies. However, we found limited of evidence and involving various study design, thus the effect of omega-3 and omega-6 on children development could not be concluded.

Figure 2. Risk of publication bias of included studies



CONCLUSION

In summary, we identified 4 articles evaluating the relationship between omega-3 and/ or omega-6 LCPUFA and children development. The findings showed that the association was only reported in observational study, whereas it was not found in experimental study. However, the included studies might have high risk of bias in generalizability. Due to limited of evidence, future studies with more robust design and methodology are notably needed to clarify the effect.

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