SYSTEMATIC REVIEW

The Growth-promoting Effect of Omega-3 on Children: a Systematic Literature Review

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ABSTRACT

Introduction: Poor growth and development can have long-term adverse health impacts, including increased birth defects, impaired cognitive function, and low academic achievement. Essential nutrients, such as omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), offer various health benefits. However, the impact of omega-3 on children's growth is under-researched, with studies typically focusing on single domains like cognitive development. This study aims to review the growth-promoting benefits of omega-3 on children across multiple growth domains. **Materials and methods:** Following PRISMA guidelines and registered with PROSPERO (CRD42023417580), three databases—PubMed, Scopus, and Cochrane Library—were searched for relevant articles from 2018 to 2022. The Cochrane Risk of Bias Tool for randomized trials (RoB2) was used to assess bias risk, and Mendeley was used to manage and deduplicate articles. **Results:** Seven randomized clinical trials (RCTs) from 2018 to 2020 were reviewed. Only one study found a significant positive impact of omega-3 on children's cognitive development, while five studies did not. One study explored neurodevelopment, and two RCTs from the UK and Spain examined behavioral outcomes. A study from Indonesia assessed physical growth. **Conclusion:** Overall, omega-3 fatty acids did not show a significant impact on early childhood development. Omega-3 supplements may enhance behavioral development and physical growth in children but do not significantly affect cognitive or neurodevelopment. *Malaysian Journal of Medicine and Health Sciences* (2025) 21(1): 282-292. doi:10.47836/mjmhs.21.1.34

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INTRODUCTION

Despite the great achievements attained by mankind in the past decades, millions of children in low- and medium-income countries have been suffering from stunted issues in their growth and development (1). A report published by the World Health Organization (WHO) in 2020 recorded that about 149.2 million (22%) children under the age of five were stunted (too short for their age) and 45.4 million children were too thin for their height (wasting), in which both serve as indicators of chronic malnutrition (2). Poor growth and development exert long-term negative health consequences, such as increased risk of birth defects, impaired cognitive function, and low academic achievement (3). In order to mitigate the long-term negative health effects on children, it is integral for children to consume all the important nutrients necessary for healthy growth. In 2012, the World Health Assembly Resolution 65.6 supported a Comprehensive Action Plan on Maternal, Infant, and Young Child Nutrition to achieve a 40% decrease in the number of stunted children under the age of five by 2025 (4). Malnutrition and deficiencies that plague children should be alleviated to achieve this objective.

Nutritional balance is an important aspect that should be ensured throughout pregnancy, breastfeeding, childhood, and later phases due to its significant impact on all stages of human development. The long-chain polyunsaturated fatty acids in omega-3 (n-3 LCPUFAs) refer to one of the vital sources of nutrients that ensure the healthy growth of fetuses and children. Studies on preclinical and clinical stages have disclosed the effect of omega-3 on both neurogenesis and growth. Neurodevelopment, including growth and cognitive development, benefits from the consumption of n-3 LCPUFAs (5). High-level omega-3 consumption during pregnancy has been associated with brain and nerve tissue development at the maximal intrauterine accretion period (6). To ensure optimum growth and development of children in the first 1000 days, all necessary nutrients, including those from dietary intake, must be supplemented in adequate amounts throughout the critical development stages (7).

As a source of nutrient, omega-3 is crucial for the growth of a child (8). Omega-3, inclusive of EPA and DHA, is a type of dietary fat that offers a range of health benefits. Both EPA and DHA are integral for optimal embryonic development (9). Several studies have outlined the benefits of DHA for pregnancy, preterm-born neonates, breastfeeding women, and brain development (3,10-12). Binder et al., (2019), for instance, found that electrophysiological brain development of preterm newborns was accelerated with DHA intake (10). Another study found that omega-3 supplementation during the last trimester of pregnancy enhanced the neurodevelopment in the first six years of life in male offspring (11).

However, specific studies that examine the growth-promoting effect of omega-3 on children are in scarcity. As most studies are limited to a single domain, such as cognitive development, other child growth aspects are dismissed. Hence, this review delved into the growth-promoting effect of omega-3 on children across various growth domains. The effect of omega-3 on child growth development in many observational studies and supplementation experiments recorded mixed results. While some studies revealed the benefits of omega-3 supplementation, others reported otherwise. The mixed results found in omega-3 supplementation studies for fetus and child growth development are ascribable to omega-3 intake with other components. Hence, a comprehensive systematic literature review was carried out to determine the growth-promoting effect of omega-3 on children.

MATERIALS AND METHODS

The review protocol and registration

The review protocol applied in this study adhered to the statement and general principle outlined in PRISMA (13). Following the review protocol, the research question was formulated first and this was followed by the systematic search strategy, the selection process, the study risk of bias assessment, and the data collection process. This systematic literature review was registered at the PROSPERO under the registration number CRD42023417580.

Formulation of research question

The formulation of the research question for this review closely adhered to the Population, Intervention, Comparison, and Outcome (PICO) tool. As a tool that guides authors to construct well-built and searchable questions for systematic literature review, PICO states the following four primary concepts: Population or Problem, Intervention or Exposure, Comparison (if any), and Outcome(s) (14). With these concepts serving as the foundation for this review, the four basic components in the study are: children (Population), omega-3 supplement (Intervention), as well as the growth and development of children (Outcome). The research question constructed for this study based on PICO is “Does the consumption of omega-3 supplement enhance the growth and development of children?”

Inclusion criteria for studies

This systematic literature review looked into the growth-promoting effect of omega-3 on children. To identify and extract the relevant articles from the databases, eligibility criteria were established by the authors. The inclusion and exclusion criteria for the eligibility process were set in accordance with the PICO framework (see Table I).

Table I: Exclusion and inclusion criteria of eligibility criteria

Criteria	Inclusion	Exclusion
Language	English	Non-English
Year of publication	2018 – 2023	< 2018
Study design	Full research text of original article of randomized or non-randomized controlled trials	Abstracts without full-text, reports, book chapters, editorials, animal studies, systematic review or any review, and meta-analysis
Population under study	Children aged between 0 and 18 years	Participants above 18 years of age, pregnant women, and fetus
Intervention	Oral omega-3 supplements in the form of capsules/tablets/pills or formula drinks.	No consumption of oral omega-3 supplement
Outcome(s) of interest	Any data that indicate relevant growth and developmental outcome domain examined via milestone achievement and/or scales/indices	No data that indicates relevant growth and developmental outcome domain examined via milestone achievement and/or scales/indices

1. Types of study

All full-text English articles published within five years prior to this study were included in the comprehensive review. Blinded and open-label RCTs, as well as non-randomized studies (cohorts and case-controls) that assessed the efficacy of omega-3 in promoting the growth and development of children, were eligible for this study. On the contrary, abstracts without full text, reports, commentaries, book chapters, editorials, animal studies, study protocol, systematic review or any review, meta-analysis, as well as studies published prior to 2018 and in a language other than English, were excluded from the review.

2. Types of participant
This review included studies that recruited children aged from 0 to 18 years as the subjects based on the definition put forward by the United Nations (1989) (15). Participants above 18 years old, pregnant women, and fetus were excluded. Participants from all countries, ethnicities, family education backgrounds, and household incomes were eligible for this study.

3. Types of intervention
In order to be eligible for this review study, omega-3 supplementation must be orally administered as capsules/tablets/pills or formula drinks as the intervention approach. The trials were deemed eligible if the intervention included the administration of omega-3 supplements in isolation or as a mixture. If the omega-3 supplementation is combined with another intervention or exposure, it should isolate the effect of omega-3 on the outcomes. Trials based on dietary advice to increase omega-3 consumption as an intervention and parenteral nutrition were disregarded. For comparator or control, other treatment approaches that promote the growth and development of children, placebo, or no comparator were accepted. Trials were incorporated in the review if an appropriate placebo was applied as control to isolate the effect of omega-3.

4. Types of outcome measure
To investigate the growth-promoting effect of omega-3 on children, all relevant growth developmental outcome domains diagnosed via assessment of milestone achievement and/or scales/indices as outcome measures were accepted. This included cognitive and behavioral development, neurodevelopment, physical growth, language or communication, attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD).

Search strategy
The comprehensive literature search was performed in three databases; Scopus, PubMed, and Cochrane. The sorting process was executed automatically based on the respective sorting function of the database. The sorting process adhered to the inclusion and exclusion criteria, which dictated the language of the study, the publication year, and the study design, to ease the process of article selection. The search process was carried out by identifying all synonyms, related terms, and variations of the main keywords used in this review, namely: growth-promoting effect, omega-3, and children. This string of keywords was applied to obtain more options and to enhance the keyword search across the selected databases to identify more relevant articles for the review based on the research question. The identification process included online thesaurus, keywords applied in past studies, as well as keywords recommended by Scopus and expert researchers, to identify all the synonyms, related terms, and variations. A comprehensive search string was applied to the selected databases by combining the selected keywords using the Boolean operators "AND" and "OR", as well as the phrase searching function (see Table II). The main search concept was linked by using the Boolean operator "AND", whereas terms within the same domain were linked by using the Boolean operator "OR". All the search procedures were performed by a single author. After that, a thorough review was performed by the other authors to eliminate bias during the review process. In the case of disagreement, a decision was achieved by the consensus of most of the authors.

Table II: Search strings and databases

Database	Search String
Scopus	TITLE-ABS-KEY ("growth promoting" OR "growth development" OR "growth effects" OR "growth impact" OR "growth outcome" OR "brain development" OR "neurodevelopment" OR "cognitive behavior" OR "cognitive development" OR "intellectual development" OR "mental development" OR "intelligence quotient" OR "IQ" OR "psychological development" OR "eye development" OR "retina development" OR "vision development" OR "heart development" OR "physical growth" OR "physical development") AND TITLE-ABS-KEY ("Eicosapentaenoic acid" OR EPA OR "Docosahexaenoic acid" OR DHA OR "omega 3") AND TITLE-ABS-KEY (kid OR children OR toddler OR baby OR infant OR newborn OR neonates OR adolescent OR preschooler OR juvenile)
PubMed	(("growth promoting" (Title/Abstract) OR "growth development" (Title/Abstract) OR "growth effects" (Title/Abstract) OR "growth impact" (Title/Abstract) OR "growth outcome" (Title/Abstract) OR "brain development" (Title/Abstract) OR "neurodevelopment" (Title/Abstract) OR "cognitive behaviour" (Title/Abstract) OR "cognitive development" (Title/Abstract) OR "intellectual development" (Title/Abstract) OR "mental development" (Title/Abstract) OR "intelligence quotient" (Title/Abstract) OR IQ(Title/Abstract) OR "psychological development" (Title/Abstract) OR "eye development" (Title/Abstract) OR "retina development" (Title/Abstract) OR "vision development" (Title/Abstract) OR "heart development" (Title/Abstract) OR "physical growth" (Title/Abstract) OR "physical development" (Title/Abstract)) AND ("Eicosapentaenoic acid" (Title/Abstract) OR EPA (Title/Abstract) OR "Docosahexaenoic acid" (Title/Abstract) OR DHA (Title/Abstract) OR "omega 3" (Title/Abstract)) AND (kid (Title/Abstract) OR children(Title/Abstract) OR toddler(Title/Abstract) OR baby(Title/Abstract) OR infant(Title/Abstract) OR newborn(Title/Abstract) OR neonates(Title/Abstract) OR adolescent(Title/Abstract) OR preschooler(Title/Abstract) OR juvenile(Title/Abstract)))

CONTINUE

Table II: Search strings and databases. (CONT.)

Database	Search String
Cochrane	(“growth promoting” (tiabkw) OR “growth development” (tiabkw) OR “growth effects” (tiabkw) OR “growth impact” (tiabkw) OR “growth outcome” (tiabkw) OR “brain development” (tiabkw) OR “neurodevelopment” (tiabkw) OR “cognitive behavior” (tiabkw) OR “cognitive development” (tiabkw) OR “intellectual development” (tiabkw) OR “mental development” (tiabkw) OR “intel-ligence quotient” (tiabkw) OR IQ (tiabkw) OR “psycho-logical development” (tiabkw) OR “eye development” (tiabkw) OR “retina development” (tiabkw) OR “vision development” (tiabkw) OR “heart development” (tiabkw) OR “physical growth” (tiabkw) OR “physical develop-ment” (tiabkw)) **AND (**“Eicosapentaenoic acid” (tiabkw) OR EPA (tiabkw) OR “Docosahexaenoic acid” (tiabkw) OR DHA (tiabkw) OR “omega 3” (tiabkw)) **AND (**Kid (tiabkw) OR children(tiabkw) OR toddler(tiabkw) OR baby(tiabkw) OR infant(tiabkw) OR newborn(tiabkw) OR neonatesOR adolescent(tiabkw) OR preschooler(-tiabkw) OR juvenile(tiabkw)

Note. (tiabkw): title or abstract or keyword; TITLE-ABS-KEY: title or abstract or keyword

Study selection

The screening process for the selected articles was carried out by adhering to the pre-defined inclusion and exclusion criteria. Two authors (MA and NZ) independently screened and combed through the title and abstract of the retrieved articles by using Microsoft Excel. The full texts of the eligible articles were independently assessed by the same reviewers from the initial phase by closely adhering to the eligibility criteria. None of the screening authors were blinded to any detail of the studies. The disagreements and discrepancies in article selection were discussed among the reviewers to ensure that the selected articles satisfied the inclusion and exclusion criteria. The authors were contacted, where appropriate, to clarify any missing or inadequate information to ascertain the eligibility of the articles. Reasons for dismissing the articles were documented at all stages of the articles selection process. The selection process was recorded in detail to complete the PRISMA flow diagram (16).

Data extraction and management

During the full-text analysis, data were extracted from the selected articles that satisfied the inclusion criteria set for this review study. The data extraction process was performed based on the research question, whereby any data obtained from the reviewed studies that could answer the research question were extracted and arranged in a table. The authors independently extracted all data from each selected article by using a form designed exclusively for this review, which was integrated with a modified version of the Cochrane Effective Practice and Organization of Care Group data collection checklist (Cochrane EPOC Group 2020) to record details pertaining to the study setting, participants and population, interventions, and outcomes (17). The general bibliographic information, including authors, publication year, and study design, was determined from the selected articles. A data extraction form was prepared for this study purpose. The disagreements and discrepancies on the extracted data were resolved through discussion and the consensus reached between the two review authors.

The domains and sub-domains of the outcomes were identified by observing the patterns and themes; clustering, counting, and highlighting the similarities, as well as by looking into the relationships that were tested in the extracted data derived from the selected articles. Upon combining the related and similar data into a group domain, a total of four group domains were identified. The authors examined any discrepancies, thoughts, puzzles, and ideas that might be associated with the interpretation of the findings while developing the outcome domain until they agreed on the adjustment of the established domain outcome and sub-domains. Summary tables of each qualitative trial and narrative synthesis are presented to compare the effect of omega-3 on the different measured outcomes.

Quality assessment of the selected studies

Two review authors (MA and NZ) independently evaluated the risk of bias in the selected trials using RoB2 (18). The authors assessed the domains, including bias arising from the randomization process, bias of deviations from the intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selecting the reported outcomes. Articles that were mutually agreed by both authors as “low-risk bias” or “some concern” were included in the review, whereas articles categorized as “high-risk bias” were discarded. The disagreements were resolved by the two authors through discussion and later with the third author if the two authors failed to agree. The risk of bias for the selected studies was visualized as a traffic-light plot by using the risk-of-bias visualization (robvis) tool (19).

RESULTS

Study selection

In total, 460 papers were identified and extracted from the three databases. In particular, 335 papers were retrieved from Scopus, 28 papers were obtained from PubMed, and 97 papers were extracted from Cochrane. After removing 91 duplicate papers prior to screening, 369 studies remained for the screening process. After screening the title and abstract of the 369 papers, 348 studies were excluded from this review due to the following reasons: animal study (n = 72), non-eligible population (n = 100), non-eligible intervention (n = 99), non-eligible outcome (n = 27), incomplete study (n = 8), systematic review (n = 15), and unrelated topic (n = 27). From the remaining 21 articles, three were disregarded as the full-text articles were not accessible and another ten were discarded during the full-text screening process due to the following reasons: non-eligible intervention (n = 5), non-eligible outcome (n = 2), incomplete study (n = 2), and brief report (n = 1). After performing full-text screening, the remaining eight articles were assessed with risk of bias assessment and one article was dismissed due to high-risk bias. As a result, the identification and screening processes revealed seven articles that met the pre-defined inclusion criteria and were eligible for further review. The PRISMA flow diagram for all database outcomes and article selection is presented in Fig. 1.

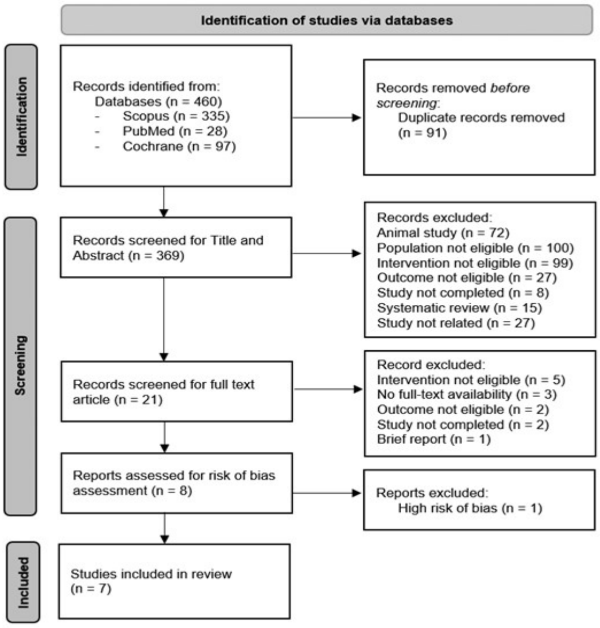

Fig. 1: PRISMA flow chart diagram of the systematic literature review strategy

Study characteristics

Seven RCTs published from 2018 to 2020 were selected for this review study. Out of the seven articles, two articles each were conducted in the UK (20,21) and Spain (20,22), while one each study was performed in Germany, Italy, Turkey (20), the Netherlands (23), Australia (24), Indonesia (25), and Iran (26). The participants in the selected articles consisted of healthy adolescents (13-15 years old) (23), children underperforming in reading skills (7-9 years old) (21), preterm infants (24), stunting children (1-3 years old) (25), children with phenylketonuria (PKU) (8-10 years old) (20), and children with ADHD (6-12 and 18 years old) (22,26). Two articles did not report the ethnicity of the participants and two studies disclosed the ethnicity of the participants; one study (25) recorded 84.7% white, 9.9% unknown, 2.4% Asian, 2.1% black, 1.3% mixed, and 0.5% others, whereas the other study (24) recruited 83.1% Caucasian and 16.9% other ethnicity. Two studies (23,24) reported that the participants had parents who possessed secondary and tertiary levels of education, one study (26) had participants with parents having tertiary-level education, and the remaining articles did not indicate parental education level.

The dose and composition of the interventions differed among the selected articles with a diverse variation. Three articles (20,21,24) used DHA alone as intervention, another three studies (22,23,26) used the combination of DHA and EPA, while the remaining study (25) did not specify the supplement composition of omega-3 for its intervention. Those interventions were delivered in the form of krill oil capsule (520 mg of EPA and 280 mg of DHA daily) (23), alga oil capsule (600 mg of DHA daily) (21), enteral emulsion (60 mg/kg DHA daily) (24), omega-3 capsule (500 or 350 mg of omega-3 daily) (25), high oleic sunflower oil and algal oil capsule (20, 43, 80, and 127 mg of DHA daily) (20), banana-flavored emulsion (1,000 mg of DHA, 90 mg of EPA, and 150 mg of DPA daily) (22), and methylphenidate with omega-3 capsule (120 mg of DHA and 180 mg of EPA daily) (26). As for the comparator, most trials used a placebo or control composed of corn oil (21), soybean oil, soya oil (24), and olive oil (26), but four articles (20,22,23,25) did not report the composition of the placebo. Table III summarizes the setting and main characteristics of the articles that were systematically reviewed in this study.

Table III: Summary of the setting and main characteristics of the selected articles

Authors	Study type	Study region	Sample size	Population	Age of participants	Intervention	Intervention composition	Exposure duration
van der Wurff et al., 2019 23)	RCT	The Netherlands	204	Healthy adolescents with omega-3 serum levels below 5%	13 to 15 years old	Krill oil capsule	520 mg EPA and 280 mg DHA	12 months
Paul Montgomery et al., 2020 (21)	RCT	The United Kingdom	372	Healthy children underperforming in reading	7 to 9 years old	Alga oil capsule	600 mg DHA	16 weeks
Erandi Hewawasam et al., 2020 (24)	RCT	Australia	73	Preterm infant	Post-natal infants	Enteral emulsion	60 mg/kg of DHA	First day of birth until 36 weeks of post-menstrual age
Lewi Jutomo et al., 2020 (25)	RCT	Indonesia	24	Stunting children	1 to 3 years old	Omega-3 capsule	350 or 500 mg of omega-3 fatty acids	60 days
Demmelmair et al., 2018 (20)	RCT	Germany, Italy, the UK, Turkey, and Spain	109	Children with PKU	8 to 10 years old	High oleic sunflower oil and algal oil capsule	20, 43, 80, or 127 mg DHA	6 months

CONTINUE

Table III: Summary of the setting and main characteristics of the selected articles. (CONT.)

Authors	Study type	Study region	Sample size	Population	Age of participants	Intervention	Intervention composition	Exposure duration
Rodríguez et al., 2019 (22)	RCT	Spain	66	Children with ADHD	6 and 18 years old	Banana-flavored emulsion	DHA 1,000 mg, EPA 90 mg, and DPA acid 150 mg	6 months
Mohammad Zadeh et al., 2019 (26)	RCT	Iran	66	Children with ADHD	6 to 12 years old	Methylphenidate with omega-3 capsules	EPA 180 mg and DHA 120 mg	2 months

Individual outcomes of the articles

1. Cognitive development

Of the seven articles, six mentioned neuropsychological test, reading, working memory and behavior, attention assessment, height measurement, cognitive performance, neurological function, fine and gross motor skills, cognitive measurement, behavioral assessment, and ADHD rating scale by parents. Only one study disclosed the statistically significant finding that the supplementation of omega-3 improved the cognitive development of children, whereas the other five studies reported that omega-3 consumption had no significant effect on the cognitive development of children. Rodrнguez et al., (2019) (22) listed the benefits of omega-3 in improving cognitive development among children. The study found that omega-3 supplementation had statistically significant improvements in omissions and response time in the visual modality ($P = 0.049$) on children diagnosed with ADHD by deploying the D2 test of attention and the AULA Nesplora (virtual) test. Nonetheless, the trial conducted in the Netherlands by van der Wurff et rodial., (2019) (23) found that omega-3 intake had no significant effect on the neurocognitive tests that included the letter digit substitution task (LDST) ($P = 0.085$), the D2 test of attention ($P = 0.175$), the digit span backward test ($P = 0.224$), the digit span forward test ($P = 0.783$), the Stroop interference test ($P = 0.321$), and the concept shifting task ($P = 0.760$). In addition, no statistically significant variance was noted between methylphenidate with omega-3 and methylphenidate with placebo on children diagnosed with ADHD based on attention deficit and hyperactivity subscales ($P \geq 0.75$) assessed using parent's ADHD rating scale (26). Turning to the study that assessed healthy children underperforming in reading, the supplementation of alga oil capsule containing 600 mg DHA for 16 weeks revealed no statistically significant variance between the treatment groups for post-intervention on reading ($P = 0.179$) and working memory (recall of digits forward, P = 0.826 and recall of digits backward, $P = 0.075$) evaluated by using the British Ability Scale (New BAS II and BAS 3) (21). Next, the study conducted by Demmelmair et al., (2018) (20) across four countries (i.e., Germany, Italy, the UK, Turkey, and Spain) also found insignificant improvement in the cognitive performance of PKU children ($P = 0.118$) despite the intake of omega-3 supplement when assessed using the Raven's Progressive Matrices (RPM). Finally, the remaining study that investigated preterm infants concluded that the supplementation of omega-3 through enteral emulsion displayed no significant difference between the DHA-supplemented group and control group assessed based on single-object task ($P = 0.510$), multiple-object task ($P= 0.230$), and distractibility task ($P = 0.860$). Moreover, the Bayley-III assessment of the cognitive score did not significantly differ between the DHA-supplemented group and the control group ($P = 0.770$) (24). Table IV summarizes the individual outcomes of the articles systematically reviewed in this study.

Table IV: Summary of the individual outcomes of the reviewed articles

Study	Population	Intervention	Outcome	Outcome measurement assessment	Finding
van der Wurff et al., 2019 (23)	Healthy adolescents with omega-3 serum levels below 5%	Krill oil capsule	Neuropsychological tests	The Letter digit substitution task (LDST), the D2 test of attention (D2), the digit Span backward and forward, the Stroop interference test, and the concept shifting task	The krill oil supplementation did not affect the cognitive measures of adolescents attending LGSE with a low baseline O3I
Paul Montgomery et al., 2020 (21)	Healthy children underperforming in reading	Alga oil capsule	Reading, working memory. and behavior	British Ability Scale (New BAS II and BAS 3), BAS II, and Corners' Rating Scale (CPRS-L)	Reading, working memory, and behavior change scores showed no consistent difference between intervention and placebo groups
Erandi Hewawasam et al., 2020 (24)	Preterm infant	Enteral emulsion	Attention	Single- and multiple-object tasks, distractibility task, and Bayley-III	DHA supplementation in infants born < 29 weeks' gestation did not affect the early development of attention. Some behavioral subscales showed minor group differences
Lewi Jutomo et al., 2020 (25)	Stunting children	Omega-3 capsule	Physical growth	Height	Omega-3 fatty acids can significantly increase the height of children under five with stunting

CONTINUE

Table IV: Summary of the individual outcomes of the reviewed articles. (CONT.)

Study	Population	Interven-tion	Outcome	Outcome measurement assessment	Finding
Demmel-mair et al., 2018 (20)	Children with PKU	High oleic sunflower oil and algal oil capsule	Cognitive performance, neurological function, as well as fine and gross motor skills	Raven's Progressive Matrices (RPM), visually evoked potentials (VEP), electrogram, and Lincoln-Oseretzky Motor Development Scale (LOS)	No significant improvement in neurological and cognitive function
Rodríguez et al., 2019 (22)	Children with ADHD	Banana-fla-vored emulsion	Cognitive and behavioral development	D2 test of attention, AULA Nesplora (virtual) test, Scale for the Assessment of Attention Deficit Hyperactivity Disorder (EDAH), and Conner's Parents Rating Scale	Omega-3 DHA dietary supplementation may be a beneficial complementary therapeutic approach in children and adolescents with ADHD
Mohammad Zadeh et al., 2019 (26)	Children with ADHD	Methylphe-nidate with omega-3 capsules	The severity of ADHD symptoms and the response rate to treatment	Parent's ADHD Rating Scale	Omega-3 had no effect on ADHD with the specified dose for 8 weeks

2. Neurodevelopment

Only a single study (20) looked into the neurodevelopment of children. The supplementation of alga oil capsule with doses ranging from 20 to 127 mg of DHA for six months exhibited a significant effect on neither neurological function (P = 0.727) nor fine and gross motor skills (P = 0.857) among children diagnosed with PKU. The study deployed visually evoked potentials (VEP), electrogram, and Lincoln-Oseretzky Motor Development Scale (LOS) as the evaluation methods. No study indicated the beneficial effect of omega-3 fatty acid supplementation on the neurodevelopment development of children in this review.

3. Behavioral development

Two RCTs from the UK and Spain examined the effect of omega-3 supplementation on children's behavioral development. Rodrнguez et al., (2019) (22) found that the supplementation of banana-flavored emulsion containing 1,000 mg of DHA, 90 mg of EPA, and 150 mg DPA significantly improved the behavior of children diagnosed with ADHD using the Scale for the Assessment of Attention Deficit Hyperactivity Disorder (EDAH) (P = 0.044) and the Conner's Parents Rating Scale (CPRS-L) (P = 0.059). A trial conducted by Paul Montgomery et al., (2020) (21) unveiled that the effect of the supplementation of alga oil capsule containing 600 mg of DHA on healthy children underperforming in reading had no statistically significant improvement of behavioral problems (P = 0.588) at post-intervention assessed using CPRS-L.

4. Physical growth

A study (25) conducted in Indonesia measured the physical growth of children following omega-3 supplementation. The trials recorded that the supplementation of omega-3 fatty acid capsules (dose: 350 or 500 mg) for stunting children displayed a significant difference in the mean score of height (P = 0.009) in the intervention group when compared to the control group after 60 days of supplementation. Seemingly, each domain development portrayed its specific dosage and exposure period (see Fig. 3).

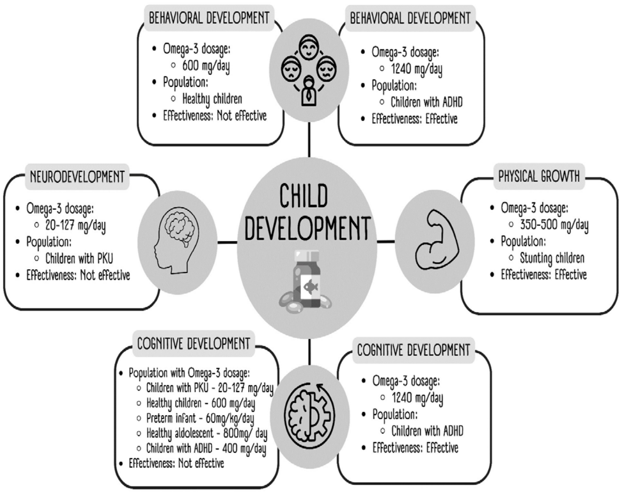

Fig. 3: Summary of results

Risk of bias

Based on the seven reviewed RCT studies, five articles (21-24,26) demonstrated low-risk bias and two articles (20,25) stated some concern regarding the risk of bias assessment using RoB2 (see Fig. 2). The five articles with low-risk bias displayed no concern or high-risk bias in each domain assessed, including bias arising from the randomization process, bias due to deviations from the targeted interventions, bias as a result of missing outcome data, bias in outcome measurement, and bias in the selection of the reported outcome. Lewi Jutomo et al., (2020) (25) stated high-risk bias due to deviations from their intended intervention because the trial had no/nil potential impact on the experimental group (randomized) and no/probable deviation from their intended intervention that balanced between the groups. In addition, the trial exhibited high-risk bias in its selection of the reported outcomes because it did not reveal information on the numerical results pertaining to selection, but merely disclosed results retrieved from the multiple eligible data analyses. Similarly, Demmelmair et al., 2018 (20) noted high-risk bias due to the deviations from their intended intervention as the trial had no/nil potential for a substantial impact (on the result) on the experimental group (randomized) but exhibited no/probable deviation from the intended intervention that balanced between the groups.

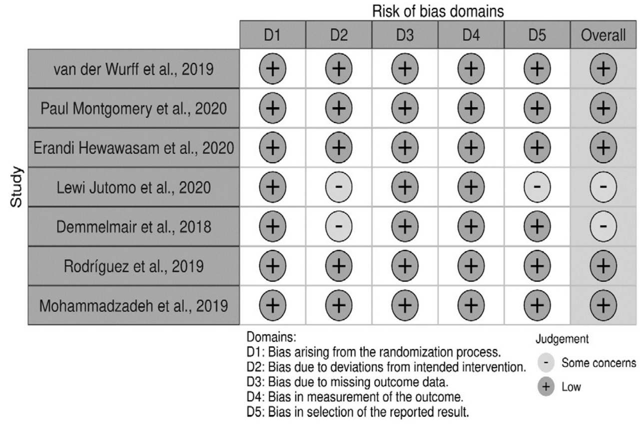

Fig. 2: Risk of bias assessed by using the Cochrane risk-of-bias tool for randomized trials

DISCUSSION

Studies on children below 18 years old did not display consistent beneficial effects of omega-3 supplementation. Apparently, five out of the seven randomized controlled intervention studies did not find any beneficial effect of omega-3 on cognitive outcome (20,21,23,24,26). This lack of positive outcome is attributable to the fact that all the reviewed RCTs had some limitation issues, including low and varying intervention doses, short intervention periods (25), small sample sizes (20,25), and no measurement of omega-3 index blood levels (25). Studies with fewer limitations also resulted in the non-beneficial effect of omega-3. The study conducted in the Netherlands, which examined one-year krill oil supplementation containing omega-3, disclosed no benefit on the cognitive effect of adolescents (23). Given that the study had the advantage of measuring the omega-3 index in the blood, participatory adherence could have been monitored throughout the experiment. In this case, non-compliance might be the reason for the negative findings because a low omega-3 index had a weak impact on the children. Turning to the study conducted by van der Wurff et al., (2020), daily supplementation of 450 mg DHA and EPA increased the omega-3 index to exceed 6% and this increased its efficacy on the cognition development of the children (27).

One of the reviewed RCTs replicated a prior paper published by the same authors. The initial experiment result displayed a positive effect on cognitive development (28), whereas the second experiment conducted by Paul Montgomery et al., (2020) showed negative outcome (21). The mixed outcomes are ascribed to the involvement of participants from different backgrounds and updated methods of outcomes measurement despite using the same study design. Hewawasam et al., (2020) reported that the researchers used high doses of DHA on infants in the previous experiment, while the follow-up study with a gap of 1 year and a half exhibited no benefit toward cognitive outcomes stemming from various extrinsic factors (24). The authors justified that the varying outcomes were attributed to the placebo group that did not receive any intervention of DHA supplementation during the postnatal period that might have resulted in developmental delay. This notion is supported by a study that stated preterm infants fed with DHA-supplemented formula milk portrayed improved visual and cognitive development within 39 months period (29).

Notably, only a single study discussed the growth-promoting effect of omega-3 on the neurodevelopment of children and it reported no beneficial outcome (20). This result is ascribable to the involvement of many study centers, despite the recorded large sample size. On the contrary, Binder et al., (2019) discovered a positive effect on the neurodevelopment of babies with extremely low birth weight who were given a mixed lipid emulsion with fish oil containing EPA and DHA, in which rapid electrophysiological brain development was observed (30). The sample size of 121 preterm newborns constituted a large cohort in a single study center at the Medical University of Vienna (Austria). As the variations in most of the amplitude-integrated electroencephalography (aEEG) parameters were statistically significant, it was impossible for other factors to influence the results. Another study revealed that in normal adolescent development, dietary omega-3 fatty acids were linked to the development of both impulse control and the function of the dorsal anterior cingulate gyrus (31).

Referring to the review, two RCTs disclosed positive results in physical growth, as well as cognitive and behavioral development, as a result of ingesting omega-3 (22,25). Rodrнguez et al., (2019) found that DHA supplementation exerted beneficial effect on ADHD children in terms of cognitive variables and behavioral development since the participants in the intervention group displayed alleviated ADHD symptoms (22). The positive effect was not only attributed to EPA and DHA because the participants were supplemented with a mixture of omega-3 fatty acids and other active ingredients, such as vitamin E and carbohydrates, which could have had an additional influence on the children. The justifications made by the authors for the study limitations provided valid evidence to the readers. The benefits of omega-3 for the physical growth of children were highlighted by Jutomo et al., (2020), as omega-3 exhibited a positive effect on the height of stunting children (25). However, evidence of the effect of omega-3 on the physical growth of children found in the current literature is in scarcity. Notably, plenty of evidence states that omega-3 can prolong gestational duration and lower the occurrence of premature birth that could lead to physical development issues, such as shorter and lighter infants. Ingesting fish oil supplements in the 30th week of pregnancy reduced the risk of premature delivery by 40% to 50%, prolonged the length of pregnancy by five days, and resulted in newborns weighing 100 grams heavier at birth (32).

It is noteworthy to highlight that this systematic literature review is the first to investigate the growth-promoting effect of omega-3 on children across a variety of domains, including neurodevelopment, cognitive and behavioral development, as well as physical growth. Despite the in-depth review conducted in this study, several limitations were observed. There is insufficient evidence to determine the dosage recommendation for children given the mixed outcomes and interventions, the limited number of studies on the subject matter, the small sample sizes, and the high-risk bias stemming from several setbacks. Overall, the reviewed articles exhibited a minimal risk of bias in terms of randomization, variations of interventions, and outcome assessments. These ambiguous outcomes are ascribed to the broad variation in the time of the outcome evaluation and the variance in demographic characteristics.

CONCLUSION

In conclusion, this review unveiled that the supplementation of omega-3 may display some benefits on the physical growth and behavioral development of children. The supplementation of omega-3 may have an impact on neither cognitive development nor neurodevelopment (see Fig. 3). However, this conclusion is debatable, uncertain, and regarded as limited due to the heterogeneity and inconsistencies of the findings, which are equivocal both within and between studies that might stem from the considerable variation in the time of the outcome evaluation.

Future research work should recruit a wider range of participants in terms of characteristics, such as ethnicity, socioeconomic background, and academic qualification, to adequately reflect the epigenetic effect variation in fatty acid metabolism on omega-3 fatty acid supplementation. In addition, future studies should identify the optimal dosage and timing of omega-3 supplementation for its maximum effect on child development. It is imminent to determine the maximum dosage and frequency of omega-3 supplementation with the least side effect tolerable by children. Lastly, more RCTs are in need to assess the consistent measurements of outcomes gathered at multiple periods throughout the development phase of children.

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