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Effect of enteral supplementation of DHA with or without ARA in preterm infants: a meta-analysis

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2024-327606).

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Received 29 June 2024
Accepted 21 March 2025

ABSTRACT

Objective This study aimed to assess whether additional enteral docosahexaenoic acid (DHA) supplementation, with or without arachidonic acid (ARA), influences morbidities diagnosed in the neonatal intensive care unit among preterm infants, excluding administration via formula or parenteral nutrition.

Design and setting This meta-analysis involved a comprehensive search of the PubMed, Embase, Web of Science and Cochrane Library databases from their inception to 9 June 2024.

Patients and interventions Randomised controlled trials focusing on the effects of enteral DHA with or without ARA in preterm infants born at ≤34 weeks gestational age or a birth weight ≤2000 g were included.

Main outcomes and measures The main outcomes included in-hospital mortality, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), sepsis, intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL).

Results Eleven trials evaluating distinct adverse outcomes in preterm infants were incorporated. Of these, nine trials assessing enteral DHA supplementation with or without ARA indicated an increased risk of BPD with a relative risk of 1.11 (95% CI 1.00 to 1.22). Additionally, five trials assessing DHA supplementation without ARA showed an increased risk of BPD with a relative risk of 1.15 (95% CI 1.03 to 1.28). No significant effects were observed on the incidence of ROP, NEC, sepsis, IVH, PVL or in-hospital mortality.

Conclusions and relevance Enteral supplementation of DHA with or without ARA did not demonstrate protective effects against major complications in preterm infants and even increased the risk of BPD. Further research is warranted to evaluate the necessity of DHA and ARA supplementation in this population.

PROSPERO registration number CRD42024552578.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Premature birth disrupts the natural maternal supply of essential fatty acids, such as docosahexaenoic acid (DHA) and arachidonic acid (ARA), which are critical for the optimal development of preterm infants.

⇒ Preterm infants usually face a high risk of complications, and exogenous supplementation of DHA and ARA is recommended to improve their outcomes.

WHAT THIS STUDY ADDS

⇒ Enteral supplementation of DHA with or without ARA did not demonstrate protective effects against major complications like retinopathy of prematurity, NEC, sepsis, intraventricular haemorrhage, periventricular leukomalacia, or in-hospital mortality in preterm infants and even increased the risk of bronchopulmonary dysplasia (BPD).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the lack of demonstrated benefits and potential risks, particularly the increased risk of BPD, the necessity and timing of enteral DHA and ARA supplementation in preterm infants should be reconsidered and further investigated.

INTRODUCTION

Preterm birth significantly impacts neonatal health, leading to adverse outcomes and placing a considerable burden on families and society.[1] Due to their immaturity, preterm infants frequently encounter complications during hospitalisation, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), sepsis, intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL), substantially heightening the risk of adverse outcomes. Among the array of supportive interventions for preterm infants, optimising ex utero nutrition as a scientific substitute for in utero nutrient provision is paramount for mitigating the risk of multiple systemic complications and ensuring optimal growth and development.

In clinical practice, polyunsaturated fatty acids (PUFAs) play a pivotal role as essential nutrients, available through breast milk, formula milk, intravenous lipid emulsions and additional single commercial products.[2] Linoleic acid and alpha-linolenic acid are essential fatty acids that require exogenous intake. Docosahexaenoic acid (DHA) and arachidonic acid (ARA), representing n-3 and n-6 PUFAs, respectively, are downstream metabolites of linoleic acid and alpha-linolenic acid, which can be synthesised endogenously or supplemented exogenously. DHA is crucial for brain development, visual acuity and cardiovascular health, while ARA plays a significant role in the inflammatory response, immune function and cell membrane integrity. In recent years, exogenous supplementation of DHA and ARA, through single commercial products, has been extensively employed in clinical settings, with the anticipation of mitigating early

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To cite: Dang D, Gao Z, Zhang C, *et al*. *Arch Dis Child Fetal Neonatal Ed* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2024-327606

adverse outcomes and ensuring favourable long-term neurological prognosis in preterm infants.[3 4]

Nevertheless, the latest systematic reviews evaluating the impact of DHA supplementation through a combination of dietary intake, intravenous lipid emulsions and additional commercial products have shown that augmenting DHA with or without ARA or other PUFAs does not significantly reduce the risk of ROP,[5 6] and single DHA supplements may even elevate the risk of NEC.[7] The findings regarding BPD are inconclusive: while DHA with or without ARA supplementation does not increase the risk, high doses of DHA may increase the incidence of BPD.[8–11] The above studies suggest that additional DHA supplementation, with or without ARA, may not be necessary. However, these studies primarily focused on a single specific condition. More importantly, the interventions in these studies included not only oral supplementation but also additional DHA or ARA administered through formula or parenteral nutrition. These two methods differ significantly in dosage, with enteral formulations uniquely increasing both the workload for healthcare providers and the financial burden on patients.

This study seeks to investigate the necessity of extra DHA supplementation, with or without ARA, in preterm infants by clarifying the association between singular enteral DHA supplementation with or without ARA and adverse outcomes in preterm infants through systematic review and meta-analysis, furnishing a theoretical foundation for the clinical application of DHA and ARA.

METHODS

The study was conducted following Cochrane Handbook procedures (V.5.1.0) and Cochrane Neonatal Review Group guidelines (https://training.cochrane.org/handbook/archive/v5.1/). Reporting was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[12] The protocol was registered with PROSPERO (CRD42024552578).

Eligibility criteria

We included randomised controlled trials focusing on preterm infants, primarily those born with a gestational age of less than 34 weeks or a birth weight of less than 2000 g, regardless of maternal supplements either before or after birth. Conference abstracts, reviews and case reports were not included.

In the intervention group, infants received enteral DHA with or without ARA within 28 days of birth, while the control group received either placebo or no intervention. Studies involving enhanced DHA with or without ARA in formula or lipid emulsions were excluded. There were no specific requirements for the dosage and duration of intervention.

Outcome measures focused on early complications in preterm infants, including BPD, ROP, NEC, sepsis, IVH, PVL and in-hospital mortality. These outcomes were assessed whether reported as primary or secondary outcomes in the included studies. The diagnostic criteria for diseases were not restricted and are detailed in online supplemental table 1.

Data sources and search strategy

The literature search was performed using databases including PubMed, Embase, Web of Science and Cochrane library from the inception of each database to 9 June 2024. The search strategy used both Medical Subject Headings and text words. Detailed search strategies for each database are provided in the online supplemental appendix 1. Duplicate records across databases were removed using ENDNOTE software.

DD and ZG independently screened titles, followed by abstracts, and finally full-text articles, to determine eligibility for inclusion. Additionally, we also manually searched the reference lists and bibliographies of included studies to identify additional relevant reports.

Data extraction and risk-of-bias assessment

DD and ZG independently extracted data from the included articles to ensure accuracy and reliability. In cases where there was disagreement over the extracted data, CZ acted as an arbiter to resolve the discrepancies and determine the final data. The data extraction process involved collecting information on the study author, study country, study year, sample size, participants (gestational age/birth weight), supplement intervention, placebo, start time of intervention, duration of interventions, and adverse outcomes of preterm infants. For assessing the risk of bias, the Cochrane risk-of-bias tool was employed.

Data synthesis and statistical analysis

Analysis was conducted using Review Manager V.5.4 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark) with a fixed-effects model and the Mantel-Haenszel method for categorical variables. Effect sizes were estimated as risk ratios (RRs) for treatment along with 95% CIs for each outcome. Between-study heterogeneity of the effect estimates was assessed by inspecting forest plots and calculating I^2 statistics. In cases of notable heterogeneity ($I^2>50\%$), potential sources were investigated. Sensitivity analysis was conducted by analysing data according to different disease severity outcomes, including moderate to severe BPD,[13 14] requiring therapy ROP, grade III-IV IVH, and confirmed NEC defined as Bell stage II or higher.[15 16] Additional subgroup analyses were conducted based on DHA alone (DHA group) and DHA combined with ARA (DHA&ARA group), as well as varying DHA dosages, with high-dose DHA defined as >60 mg/kg/day. Funnel plots were used to assess publication bias. A two-sided value of $p<0.05$ was considered statistically significant.

Quality assessment of pooled analysis

We used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system[17] to assess the quality of evidence for each unique pooled analysis, categorising them as 'high', 'moderate', 'low' or 'very low'. Of the eight criteria established by the GRADE method, five—risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias—can undermine confidence in the accuracy of effect estimates, which may lead to downgrading.

RESULTS

Trial selection and characteristics

We initially identified a total of 9707 relevant articles through our comprehensive search strategy. After applying our inclusion and exclusion criteria, 19 articles were thoroughly evaluated. We excluded one article[18] due to the absence of outcome variables and four articles[19–22] due to duplicate data from the same studies. Consequently, data from 14 articles[23–36] representing 11 unique trials were included (figure 1).

These 11 trials encompassed a cohort of 2567 preterm infants from 10 different countries. Detailed study characteristics are provided in table 1. Specifically, 9 studies focused on BPD, 8 studies addressed ROP, 10 focused on NEC, 8 on sepsis, 7 on

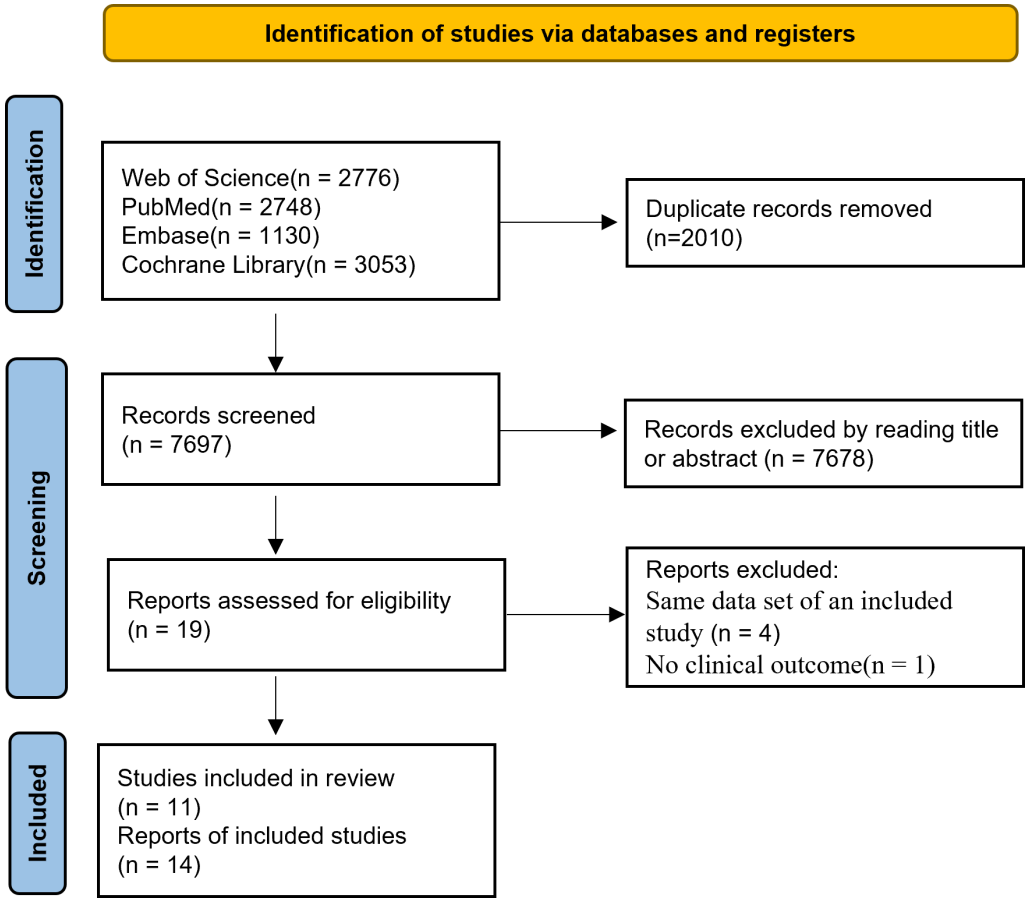

Figure 1 Flow chart of search results.

IVH, 4 on PVL and 4 on in-hospital mortality. The dosages of DHA varied across studies from 20 mg/kg/day to 1.2 g/day, and ARA dosages from 40 mg/kg/day to 240 mg/kg/day. The intervention typically began within the first 7 days of life and continued for 14 days, up to 36 weeks or 40 weeks of corrected gestational age, or until discharge.

Among the 11 included trials, 3[23 33 35] were assessed as having some concerns regarding bias, while 8[26–32 34 36] were considered to have a low risk of bias. No studies were identified as having a high risk of bias (figure 2). Funnel plot demonstrated no evidence of significant publication bias (online supplemental figure 1).

Data synthesis on complications in preterm infants

A comprehensive data synthesis analysis was performed to evaluate the impact of enteral DHA with or without ARA supplementation on the risk of early complications in preterm infants, including BPD, ROP, NEC, sepsis, IVH, PVL and in-hospital mortality (table 2 and online supplemental figure 2.1–2.7). The findings revealed varied effects of DHA with or without ARA on these conditions. Notably, the analysis of nine studies[23 26 28–32 34 35] encompassing 2272 infants indicated an increased risk of BPD associated with supplementation (RR: 1.11; 95% CI 01.00 to 1.22; I^2=0). Meanwhile, five studies[23 26 30 33 34] on any ROP found no significant link between DHA with or without ARA and the occurrence of ROP (RR: 0.96; 95% CI 0.84 to 1.10; I^2=0). The pattern of no significant association continued with other complications: 10 studies[23 26 28 29 31–36] involving 2457 infants showed no correlation with NEC (RR: 1.00; 95% CI 0.74 to 1.33; I^2=7%), 8 studies[23 26 28–31 34 35] involving 2244 infants found no link with sepsis (RR: 0.95; 95% CI 0.85 to 1.06; I^2=20%), and 7 studies[24 26 28 29 31 34 35] involving 2245 infants reported no connection with IVH (RR: 1.03; 95% CI 0.91 to 1.16; I^2=21%). Similarly, four studies[26 28 34 35] involving 1866 infants demonstrated no relationship with PVL (RR: 0.76; 95% CI 0.39 to 1.49; I^2=0). Lastly, the analysis of four studies[23 28 34 35] including 2060 infants indicated that DHA with or without ARA did not affect in-hospital mortality rates (RR: 1.11; 95% CI 0.83 to 1.49; I^2=53%). Overall, while DHA with or without ARA appears to increase the risk of BPD, it shows no significant impact on other major complications in preterm infants.

Subgroup analyses

Analyses of the stratified subgroups revealed an increased risk of BPD in preterm infants in the DHA group (RR: 1.15; 95% CI 1.03 to 1.28; I^2=0). However, the risk of BPD did not increase in the DHA&ARA group, and no correlation was observed between the DHA or DHA&ARA groups and the occurrence of ROP, NEC, sepsis, IVH, PVL, or in-hospital death (table 3 and online supplemental figure 2.1–2.7).

Analyses of the stratified groups based on high-dose and low-dose DHA with or without ARA revealed that the risk of BPD increased in the high-dose DHA group (RR: 1.27; 95% CI 1.02 to 1.60; I^2=0). Although the low-dose group did not show a statistically significant increase, there was a clear trend towards higher risk (RR: 1.06; 95% CI 0.96 to 1.18; I^2=0). No correlation was observed between DHA dosage and the occurrence of ROP, NEC, sepsis, IVH, PVL or in-hospital death (table 3 and online supplemental figure 3.1–3.7).

Table 1 Characteristics of included studies

Study	Country	Year	Sample size	Populations (GA/BW)	Supplement intervention	Placebo	Start of intervention	Duration	Outcomes
Hellström *et al* Pivodic *et al* Wackernagel *et al*[23–25]	Sweden	2021	209	<28 weeks	DHA 50 mg/kg/day ARA 100 mg/kg/day	No supplementation	Within 72 hours after birth	Until 40 weeks CA	BPD, ROP, NEC, sepsis, IVH, in-hospital mortality
Moltu *et al* Wendel *et al*[26 27]	Norway	2024	120	<29 weeks	DHA 50 mg/kg/day ARA 100 mg/kg/day	Medium chain triglycerides	Second day of life	Until 36 weeks CA	BPD, ROP, NEC, sepsis, IVH, PVL
Collins *et al*[28]	Australia, New Zealand and Singapore	2017	1273	<29 weeks	DHA 60 mg/kg/day	Soy emulsion	Within 3 days after birth	Until 36 weeks CA	BPD, ROP, NEC, sepsis, IVH, PVL, in-hospital mortality
Frost *et al*[29]	Chicago	2021	30	<1500 g	DHA 40 mg/kg/day ARA 80 mg/kg/day; or DHA 120 mg/kg/day ARA 240 mg/kg/day	Sunflower oil	Within the first 72 hours of life	8 weeks	BPD, NEC, ROP, sepsis, IVH
Bernabe-Garcia *et al*[30]	Mexico	2019	110	<1500 g and ≥1000 g	DHA 75 mg/kg/day	Sunflower oil	–	14 days	BPD, ROP, sepsis
Robinson *et al*[31]	Chicago	2021	30	<1000 g and <34 weeks	DHA 20 mg/kg/day ARA 40 mg/kg/day; or DHA 60 mg/kg/day ARA 120 mg/kg/day	Sunflower oil oil	–	8 weeks or discharge	BPD, ROP, NEC, sepsis, IVH
Collins *et al*[32]	Australia	2015	40	<33 weeks	DHA 40 mg/kg/day, 80 mg/kg/day or 120 mg/kg/day	Tuna oil	–	28 days	BPD, NEC
Bernabe-García *et al*[33]	Mexico	2021	225	<1500 g and ≥1000 g	DHA 75 mg/kg/day	Sunflower oil	–	14 days	NEC
Marc *et al*[34]	Canada	2020	528	23–28 weeks	DHA 1.2 g/d	A mix of corn and soy oils	Within 72 hours of life	Until 36 weeks CA	BPD, ROP, NEC, sepsis, IVH, PVL, in-hospital mortality
Baack *et al*[35]	USA	2017	60	24–34 weeks	DHA 50 mg/d	Medium chain triglyceride	During the first week of life	Until discharge or 36 weeks CA	BPD, ROP, NEC, sepsis, IVH, PVL, in-hospital mortality
Fadl *et al*[36]	Egypt	2021	60	≤32 weeks or ≤1500 g	DHA 100 mg/d	No supplementation	Begin enteral feeding	14 days	NEC

ARA, arachidonic acid; BPD, bronchopulmonary dysplasia; BW, birth weight; CA, correct gestational age; DHA, docosahexaenoic acid; GA, gestational age; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Sensitivity analyses

Analyses of stratified subgroups focusing on the severity of diseases in preterm infants who received DHA with or without ARA revealed the following: supplementation with DHA with or without ARA increased the risk of moderate-to-severe BPD (RR: 1.11; 95% CI 1.00 to 1.24; $I^2=0$). There was no correlation between DHA supplementation and the occurrence of ROP requiring therapy, Bell stage II or higher NEC or grade III-IV IVH (table 3 and online supplemental figure 4.1–4.4).

DISCUSSION

This study systematically reviewed the relationship between enteral DHA with or without ARA and various complications in preterm infants. Unfortunately, the findings revealed that, while there was no increased risk of mortality, ROP, NEC, sepsis, IVH or PVL, the expected protective effects against these conditions were also not observed. Furthermore, the supplementation even increased the risk of BPD, challenging the clinical application of enteral DHA and ARA in preterm infants.

In contrast to previous meta-analyses, this study uniquely focuses on preterm infants as the primary subjects of investigation and examines the effects of enteral supplementation specifically involving DHA with or without ARA. This sets it apart from earlier research efforts that amalgamated interventions, such as prenatal or postnatal supplementation in preterm mothers, increased dose of DHA or ARA in formula milk, or modifications in lipid emulsion content, which were not strictly enteral supplementation. The objective of this study is to provide a clear understanding of the clinical benefits or potential risks associated with additional enteral supplementation in preterm infants.

Prior systematic reviews have revealed divergent findings concerning the impact of DHA with or without ARA supplementation on the incidence of BPD in mothers or preterm infants receiving elevated doses via oral, formula or intravenous lipid emulsions. While some reviews indicate no significant correlation with BPD occurrence,[8 10 11] one study hints at a potential heightened risk associated with high doses of DHA.[9] However, our study aligns with recent meta-analytical evidence indicating that enteral high-dose DHA with or without supplementation may elevate the risk of BPD. Notably, we also observed a concerning trend towards increased BPD risk in the low-dose DHA group, with a calculated RR of 1.06 (95% CI 0.96 to 1.18). Potential mechanisms underlying the observed heightened BPD risk associated with DHA supplementation warrant exploration. Given DHA's classification as a type of PUFA, it is conceivable that supplementation may augment the production of lipid peroxides and other oxidative stressors,[37] contributing to pulmonary injury and inflammation. Furthermore, despite DHA's recognised anti-inflammatory properties, supplemental intake may disrupt the delicate equilibrium between anti-inflammatory and proinflammatory pathways,[38] thereby exacerbating lung injury and predisposing to BPD development.

In the context of NEC, previous studies have suggested that DHA supplementation alone increases the risk of NEC, while the combination of DHA and ARA appears to reduce this risk.[7] However, our study suggests that no protective or harmful effects were observed with either singular or combined

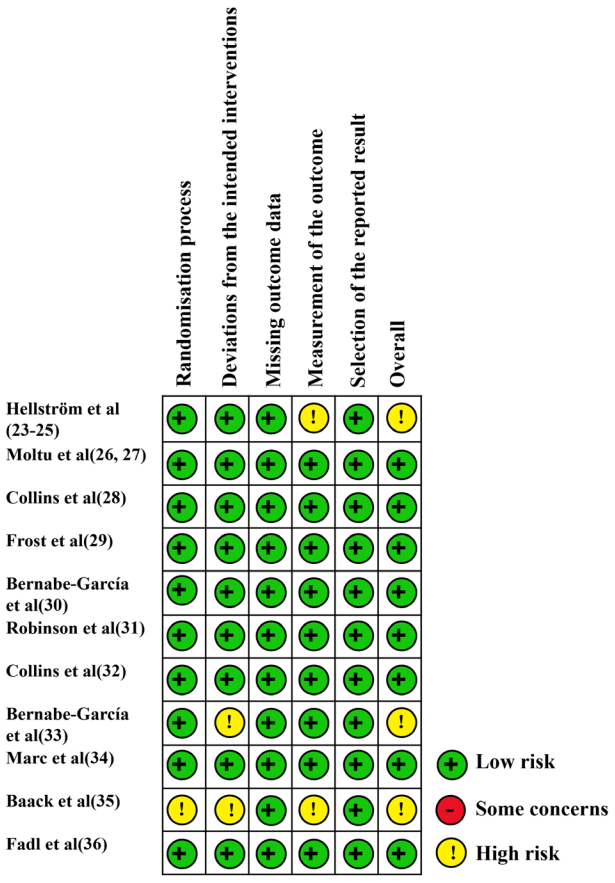

Figure 2 Risk-of-bias assessment of individual trials.

supplementation. Our findings also did not reveal a protective effect against NEC onset, as reported in the animal study.[39] Consistent with previous meta-analyses on ROP,[5 6] our investigation indicates that enteral supplementation of DHA with or without ARA fails to mitigate the risk of ROP or the necessity for treatment. Additionally, we found no significant correlation between enteral supplementation of DHA with or without ARA and the occurrence of IVH, PVL, sepsis or death, which has been rarely reported previously.

Some researchers posit that exclusive DHA supplementation may perturb the delicate balance of n-3 and n-6 PUFAs metabolism,[40] potentially culminating in adverse outcomes. They advocate for combined DHA and ARA supplementation to uphold PUFA homoeostasis and avert the onset of diseases. Nevertheless, our study indicates that combined administration of DHA and ARA does not confer a reduced risk of adverse outcomes among preterm infants.

Based on our study findings and recent assessments, the clinical utilisation of DHA and ARA warrants re-evaluation. DHA and ARA, as vital components of neuronal and photoreceptor cell membrane phospholipids, were initially intended to enhance neurological and visual development. However, two crucial considerations emerge: first, our study indicates that enteral supplementation of DHA and ARA, as well as recent practices of fortifying DHA and ARA through formula feeding or intravenous nutrition, did not ameliorate the risk of early complications in preterm infants. Second, existing research suggests that supplementing with DHA and ARA does not yield significant improvements in neurological outcomes for preterm infants.[41 42] Henceforth, given the risks of early onset diseases, the substantial expense of these products, and the increased workload for healthcare providers associated with administering medications, the necessity and timing of DHA and ARA supplementation in preterm infants merit further investigation.

The study possesses several limitations. First, in this meta-analysis, variations in DHA and ARA dosage and duration may have influenced the generalisability of the results and the ability to draw definitive conclusions. Second, discrepancies in the definition of outcomes for preterm infants across the included studies may have hampered data integration and result comparability. Third, there is a lack of clarity regarding the type of intravenous lipid emulsion administered, if any, as well as insufficient information about the composition of the enteral lipid emulsions, which may contain other fatty acids, although in smaller amounts. Additionally, the ratio of DHA to ARA warrants further analysis. Lastly, it is noteworthy that the baseline levels of DHA and ARA in the study subjects, encompassing preintervention, during intervention and postintervention phases, were inadequately delineated. Some studies suggest that high levels of DHA with or without ARA are associated with a lower risk of BPD.[19] The ambiguity in the baseline levels of DHA engenders uncertainties regarding whether the additional supplementation adequately compensated for any deficiency, whether exogenous supplementation disrupted normal metabolism, or even led to potential oversupplementation. Addressing these uncertainties should constitute a priority for future research endeavours.

Table 2 Enteral supplementation of DHA with or without ARA and adverse outcomes in preterm infants

	No of studies	Participants	RR (95% CI)	Heterogeneity (I^2(%)/*P* value)	GRADE	Comments
BPD	9	2272	1.11 (1.00 to 1.22)	0/0.44	High certainty	Initial level high
ROP	6	1163	0.96 (0.84 to 1.10)	0/0.66	High certainty	Initial level high
NEC	10	2457	1.00 (0.74 to 1.33)	7/0.38	Moderate certainty	Initial level high, downgraded due to a wide CI
Sepsis	8	2244	0.95 (0.85 to 1.06)	20/0.27	High certainty	Initial level high
IVH	7	2245	1.03 (0.91 to 1.16)	21/0.27	High certainty	Initial level high
PVL	4	1866	0.76 (0.39 to 1.49)	0/0.80	Moderate certainty	Initial level high, downgraded due to a wide CI
In-hospital mortality	4	2060	1.11 (0.83 to 1.49)	53/0.10	Low certainty	Initial level high, downgraded due to a wide CI and a high heterogeneity

GRADE Working Group grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
ARA, arachidonic acid; BPD, bronchopulmonary dysplasia; DHA, docosahexaenoic acid; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Table 3 Subgroup and sensitivity analyses of DHA with or without ARA supplementation on adverse outcomes in preterm infants

	No of studies	Participants	RR (95% CI)	Heterogeneity (I^2(%)/P value)	GRADE	Comments
BPD						
DHA	5	1898	1.15 (1.03 to 1.28)	0/0.58	High certainty	–
DHA&ARA	4	374	0.93 (0.74 to 1.16)	0/0.44	Moderate certainty	Downgraded due to a wide CI
High dose DHA	4	631	1.27 (1.02 to 1.60)	0/0.62	Moderate certainty	Downgraded due to a wide CI
Low dose DHA	7	1658	1.06 (0.96 to 1.18)	0/0.45	High certainty	Initial level high
Severe BPD	4	1972	1.11 (1.00 to 1.24)	62/0.05	Moderate certainty	Downgraded due to high heterogeneity
ROP						
DHA	4	847	1.01 (0.86 to 1.19)	0/0.70	High certainty	–
DHA&ARA	2	316	0.85 (0.67 to 1.08)	0/0.51	Low certainty	Downgraded due to a wide CI and a small sample size
High dose DHA	3	787	1.00 (0.85 to 1.18)	0/0.55	Low certainty	Downgraded due to a small sample size
Low dose DHA	3	376	0.88 (0.70 to 1.11)	0/0.59	Low certainty	Downgraded due to a wide CI and a small sample size
Require therapy ROP	5	1844	0.95 (0.68 to 1.33)	0/0.70	Moderate certainty	Downgraded due to a wide CI
NEC						
DHA	6	2073	1.00 (0.73 to 1.38)	53/0.08	Low certainty	Downgraded due to a wide CI and a high heterogeneity
DHA&ARA	4	384	0.96 (0.48 to 1.92)	0/1.00	Moderate certainty	Downgraded due to a wide CI
High dose DHA	5	800	0.70 (0.39 to 1.24)	63/0.04	Moderate certainty	Downgraded due to a wide CI and a high heterogeneity
Low dose DHA	7	1674	1.12 (0.80 to 1.57)	0/1.00	Moderate certainty	Downgraded due to a wide CI
Confirmed NEC	4	1017	0.93 (0.55 to 1.57)	44/0.15	Moderate certainty	Downgraded due to a wide CI
Sepsis						
DHA	4	1895	0.98 (0.87 to 1.10)	27/0.25	Low certainty	–
DHA&ARA	4	349	0.84 (0.66 to 1.07)	0/0.59	Moderate certainty	Downgraded due to a wide CI
High dose DHA	3	619	1.07 (0.91 to 1.24)	17/0.30	High certainty	–
Low dose DHA	6	1631	0.88 (0.76 to 1.02)	0/0.94	High certainty	–
IVH						
DHA	3	1861	1.02 (0.90 to 1.17)	65/0.06	Moderate certainty	Downgraded due to a high heterogeneity
DHA&ARA	4	384	1.04 (0.79 to 1.39)	0/0.60	Moderate certainty	Downgraded due to a wide CI
High dose DHA	2	546	0.81 (0.64 to 1.02)	11/0.29	Low certainty	Downgraded due to a wide CI and a small sample size
Low dose DHA	6	1705	1.12 (0.97 to 1.29)	0/0.88	Moderate certainty	Downgraded due to a wide CI CI
III-IV IVH	4	2127	0.85 (0.65 to 1.13)	74/0.008	Low certainty	Downgraded due to a wide CI and a high heterogeneity
PVL						
DHA	3	1746	0.80 (0.40 to 1.59)	0/0.70	Moderate certainty	Downgraded due to a wide CI
DHA&ARA	1	120	0.33 (0.01 to 8.02)	–	Low certainty	Downgraded due to a wide CI and a small sample size
High dose DHA	1	482	0.67 (0.24 to 1.91)	–	Low certainty	Downgraded due to a wide CI and a small sample size
Low dose DHA	3	1384	0.84 (0.35 to 2.00)	0/0.65	Moderate certainty	Downgraded due to a wide CI
In-hospital mortality						
DHA	3	1856	1.04 (0.75 to 1.45)	63/5.39	Low certainty	Downgraded due to a wide CI and a high heterogeneity
DHA&ARA	1	204	1.50 (0.78 to 2.89)	–	Low certainty	Downgraded due to a wide CI and a small sample size
High dose DHA	1	523	0.59 (0.32 to 1.07)	–	Low certainty	Downgraded due to a wide CI and a small sample size
Low dose DHA	3	1537	1.39 (0.99 to 1.97)	0/0.87	Moderate certainty	Downgraded due to a wide CI

GRADE Working Group grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
ARA, arachidonic acid; BPD, bronchopulmonary dysplasia; DHA, docosahexaenoic acid; DHA&ARA, DHA combined with ARA; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; RR, risk ratio.

CONCLUSIONS

The study systematically reviewed the association between enteral supplementation of DHA, with or without ARA, and various complications in preterm infants. While no benefits were observed in improving outcomes related to mortality, BPD, ROP, NEC, sepsis, IVH and PVL, the anticipated protective effects were also not evident. In fact, under specific conditions, DHA supplementation was found to increase the risk of BPD. Therefore, considering the lack of demonstrated benefits, alongside the potential risks and economic burden, further investigation into both the necessity and optimal timing of DHA and ARA supplementation in preterm infants is warranted.

Contributors HW is the guarantor. DD: study concept and design, development of methodology, analysis and interpretation of data, writing of the original draft, read and approved the final paper. ZG: study concept and design, technical and material support, read and approved the final paper. CZ: technical support, read and approved the final paper. XM and XL: analysis and interpretation of data, statistical analysis, read and approved the final paper. HW: study concept and design, project administration, writing of the review and editing, read and approved the final paper.

Funding This study was funded by the National Natural Science Foundation of China (82271737, 82301952); Jilin Provincial Department of Science and Technology (YDZJ202301ZYTS070, 20130402013GH, YDZJ202501ZYTS670).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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