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High doses of enteral docosahexaenoic acid omega-3 supplementation for prevention of bronchopulmonary dysplasia in very preterm infants: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Docosahexaenoic acid (DHA) supplementation in the neonatal period has been proposed to prevent bronchopulmonary dysplasia (BPD) in very preterm infants. We aim to determine the effects of an enteral supplementation with high doses of DHA on the risk for BPD at 36 weeks' postmenstrual age (PMA) in very preterm infants born less than 29 weeks' gestation compared with a control.

Methods and analysis We will conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) searching PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, MedRxiv, ClinicalTrials.gov (up to 1 November 2021) as well as reference lists and citations of included articles and previous reviews. RCTs targeting infants born less than 29 weeks' gestation and evaluating the effect of high doses of DHA enteral supplementation in the neonatal period compared with a control will be eligible. Primary outcome will be BPD defined as the need for oxygen and/or ventilation at 36 weeks' PMA. Two authors will independently screen for inclusion, extract data and assess data quality using the Cochrane instrument (risk-of-bias tool 2.0). We will perform meta-analysis using random effects models. Prespecified subgroup analyses are planned for the infant gestational age and sex, the marine source of DHA, mode of administration and duration of exposure. Sensitivity analysis will be performed according to the accuracy of the BPD definition (ie, physiological definition) and according to the risk of bias of the RCTs.

Ethics and dissemination This protocol for a systematic review and meta-analysis does not require ethics approval, as no primary data are collected. This study will assess the effectiveness of high doses of enteral DHA supplementation on BPD and provide evidence to clinicians and families for decision-making. Findings will be disseminated through conferences, media interviews and publications to peer review journals.

PROSPERO registration number CRD42021286705.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist and the Cochrane handbook.
⇒ This review only includes randomised controlled trials, which could limit the evidence by excluding observational studies.
⇒ The search strategy was developed specifically for each database, using controlled vocabulary and text words with no language or date restrictions.
⇒ The risk of bias will be evaluated using the revised Cochrane risk-of-bias tool for randomised trials.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a disabling chronic respiratory condition that occurs in about 45% of infants born below 29 weeks' gestation. BPD clinically presents with a need for supplemental oxygen or respiratory support that persist beyond the neonatal period. For these vulnerable infants at risk of BPD, the neonatal period is a critical time that can set the stage for lifelong morbidities such as respiratory diseases and cognitive, motor and behavioural impairments.[1–4] During this time, preventive measures can have a great and lasting impact. Omega-3 docosahexaenoic acid (DHA) could modulate inflammation and oxidative stress, which are both involved in the development of BPD.[5–7] Enteral supplementation with high doses of DHA in the neonatal period (above the amount of DHA usually found in breast milk or preterm infant formula) has been suggested to prevent BPD and to improve neurodevelopment in infants born very

preterm.[8 9] Such interventions, providing DHA above the standard nutritional DHA amounts resulting from maternal diet, supplementation recommendations or commercial formula specifically for preterm infants, are expected to cover the need for DHA accretion rate in preterm infants.[10]

Establishing a causal link between exposure to omega-3 lipids and BPD in high-risk preterm infants has important clinical implications in neonatal care. Benefits of DHA on BPD are biologically plausible, given the positive impact of DHA on inflammation[6 7 11] and the lung architecture of animals.[12 13] Moreover, observational studies showed that higher levels of DHA in the neonatal period are associated with a reduced proportion of chronic lung disease in very preterm infants.[5] On the contrary, previous reviews failed to see an effect of DHA supplementation on the risk of BPD at 36 weeks' postmenstrual age (PMA).[14–16] However, the most recent reviews did not focus on extremely preterm infants who have the highest risk for BPD or on particular groups based on the mother's or child's characteristics. Furthermore, they did not address the possible heterogeneity effects of DHA supplementation according to either the mode of administration, the source, the dosage (eg, higher dose than standard practice) as being an important factor to consider when assessing the impact of DHA on BPD in very preterm infants.[17] Indeed, post hoc analyses of a previous trial using a supplementation with a high dose of DHA suggested a potential benefit of DHA on the need for oxygen in low birth weight infants exposed to a higher risk of BPD.[9] On this basis and biological plausibility, two recent trials were specifically designed to evaluate the superiority of high doses of enteral DHA supplementation on the risk of BPD compared with a control. However, they did not show any benefit and even showed an increased risk for BPD in very preterm infants.[18 19] Nevertheless, exploratory results from these recent randomised controlled trials (RCTs) reported that sex, gestational age or mode of delivery could modulate the effect of DHA on BPD. Therefore, a clinical equipoise remains due to uncertainty on the balance of harms and benefits of high doses of DHA on BPD in the very preterm infants.

While potential benefits of high doses of DHA supplementation have been reported for neurodevelopment of infants born very preterm and is still in evaluation,[20–24] it is important to review the literature and quantify the impact of DHA on BPD in very preterm infants who are at high risk of BPD. Clarification of this effect is needed in order to improve nutritional care in neonatal intensive care units and to help appropriately counsel the mothers of these children born very preterm who may decide to take over-the-counter DHA products.

Objective

The objective of this study is to assess the effectiveness of high doses of enteral DHA supplementation on the risk for BPD at 36 weeks' PMA in very preterm infants born less than 29 weeks' gestation compared with a control.

METHODS AND ANALYSIS

Protocol and registration

This protocol has been developed with the participation of a multidisciplinary team of experts including neonatologists, nutritionists, epidemiologists and research methodologists using methodological approaches outlined in the Cochrane Handbook for Systematic Review of Interventions.[25] The protocol was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for protocol statement 2015 and planned according to the criteria of PRISMA 2020 statement.[26–29] It has been registered in the PROSPERO database with number CRD42021286705. The study is planned to start in November 2021 and end in November 2022.

Eligibility criteria

We will consider all individual or cluster RCTs assessing the effects of a high dose of enteral DHA omega-3 supplementation on BPD at 36 weeks' PMA in infants born very preterm. Very preterm infants are defined as infants born with a gestational age of less than 29 weeks' gestation. We will consider only studies with the intervention starting after birth through the neonatal period. Enteral routes for DHA administration will include (1) direct enteral supplementation to the preterm; (2) exogenous supplementation of human milk or formula and (3) enrichment of human milk through maternal DHA supplementation. Intravenous DHA supplementation will not be considered in this review, since DHA-rich intravenous lipids are administered for different objectives and would conduct to specific recommendations.[30] However, since such intravenous lipids emulsions may currently be part of routine standard care in some neonatal care units, a description of such cointerventions as part of standard care will be reported. More generally, any cointerventions that could provide DHA as part of routine practice will be reported. For the purpose of this review, we will compare intervention targeting high dose of DHA enteral supplementation (alone or in conjunction with other long-chain polyunsaturated fatty acid (LCPUFA)) in addition to standard care with a control (eg, placebo or low dose of DHA supplementation) plus standard care. A high enteral dose of DHA is defined as a dose meeting in utero accretion estimate. Therefore, we will exclude RCTs with interventions evaluating a direct enteral DHA supplementation of less than 40 mg/kg/day or a DHA supplementation through enriched milk with a targeted DHA percentage of 0.40% of total fatty acids or less. Indeed, the amounts of DHA evaluated in early RCTs aimed to achieve similar concentrations as in maternal term breast milk, which is below the estimated in utero accretion rate and may not be appropriate for very premature infants whose requirements are higher.[10] Moreover, current DHA-enriched formula offered to premature infants in standard care could achieve such low to moderate levels of DHA as well as the DHA content in maternal breast milk in Western countries.[31 32]

Table 1 PubMed search strategy

	Search
#1	"Fatty Acids, Omega-3"(Mesh:NoExp) OR "Docosahexaenoic Acids"(Mesh) OR "Fish Oils"(Mesh:NoExp) OR "Fatty Acids, Essential"(Mesh:noexp)
#2	Omega 3(TIAB) OR n 3 fatty acid(TIAB) OR n 3 Oil(TIAB) OR n3 Oil(TIAB) OR Polyunsaturated Fatty Acid*(TIAB) OR polyunsaturated FA(TIAB) OR Docosahexaenoic Acid*(TIAB) algae oil(TIAB) OR alga oil(TIAB) OR algal oil(TIAB) OR marine oil(TIAB) OR fish oil(TIAB) OR essential fatty acid*(TIAB) OR DHA(TIAB)
#3	"Infant, Premature"(Mesh) OR "Infant, Low Birth Weight"(Mesh) OR "Premature Birth"(Mesh) OR "Infant, Newborn"(Mesh)
#4	Premature Infant*(TIAB) OR preterm infant(TIAB) OR preterm infants(TIAB) OR low birth weight(TIAB) OR preterm birth(TIAB) OR preterm births(TIAB) OR Premature Birth(TIAB) OR Premature Births(TIAB) OR newborn(TIAB) OR newborns(TIAB) OR neonates(TIAB)
#5	((randomised controlled trial(pt)) OR (controlled clinical trial(pt)) OR (randomized(tiab) OR randomised(tiab)) OR (placebo(tiab)) OR (drug therapy(sh)) OR (randomly(tiab)) OR (trial(tiab)) OR (groups(tiab)))
#6	animals (Mesh) NOT humans (Mesh)
#7	(#1 OR #2) AND (#3 OR #4) AND #5 NOT #6

To be included in this review, the definition of BPD has to be related to the need for oxygen and/or ventilation at 36 weeks' PMA. Studies will also be included if they did not include data on our primary outcome but included at least one of the following secondary outcomes: death, BPD severity or BPD-free survival.

Information source and search strategy

We will search PubMed, Embase, Web of Science and specialised sites (eg, Cochrane Central Register of Controlled Trials, MedRxiv, ClinicalTrials.gov) up to 1 November 2021. The search strategy will use controlled vocabulary (eg, MeSH terms) and text words and will be adapted for each database. The search strategy for PubMed is presented in table 1. We will develop search strategies with terms related to the intervention (omega-3) and the target population (preterm). We will also use a filter to search for RCTs and human studies.[33] There will be no language or date restrictions. Finally, we will look at reference lists and citations of relevant articles (previous reviews and included studies) to identify any additional eligible studies. All citations will then be combined and duplicates excluded. Conference abstracts, reviews or case reports will not be considered.

Study selection

We will perform screening of all potentially relevant citations and references in duplicate with disagreements resolved by consensus between the two independent reviewers (IM and EP) and third-party adjudication when consensus cannot be reached. Screening will be performed in two stages, initially reviewing titles and abstracts, and then full texts for possibly relevant manuscripts. We will capture reasons for full-text exclusion. To avoid duplicate, authors, data collection date, sample sizes and study results will be compared. If needed, we will check summary tables with the trial protocol and latest trial report or publication. We will rely on researchers or translators to translate abstracts and articles not in English or French. To facilitate collaboration among reviewers, literature search results will be uploaded to Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia (available at www.covidence.org).

Data collection process

After completion of the selection process, two research team members (EP and NMPH) will independently extract information from included articles using a data extraction form, which will be pilot tested on two studies and refined accordingly. They will independently check included trials for missing data, internal data consistency, randomisation integrity (balance of patient characteristics at randomisation, pattern of randomisation), follow-up and censoring. We will solve any discrepancies with a senior research team member (IM). If required, we will contact study authors to confirm relevant information or request unpublished data (up to two emails to all authors).

Data items

We will extract (1) characteristics and methods: study design, year and country of the study and language of publication, funding source, authors' self-reported conflict of interest, registration, randomisation, setting, study population with inclusion and exclusion criteria as well as number of eligible, recruited and followed-up subjects in each trial arm; (2) interventions and control characteristics: source and type of DHA and control supplementation, doses, mode of administration, adherence to intervention, timing from birth and duration of administration and (3) outcomes: definitions and criteria used for BPD and for each secondary outcomes.

Outcomes and priorisation

The primary outcome of interest will be BPD defined as the need for oxygen and/or ventilation at 36 weeks' PMA. Dichotomous outcomes (BPD, BPD-free survival and death) are defined by the presence or absence of the diagnosis based on the best standard criteria or the criteria as reported in the studies. When more than one category is available for a given neonatal outcome (eg, none, mild, moderate, severe for BPD severity) and when these categories are mutually exclusive, we will combine numbers to provide an effect estimate for 'any definition' of the neonatal outcome. Otherwise, we will extract data matching with the more severe category of the outcome. If there are more than two comparison groups (eg, different sources of LCPUFA and a control), we will combine the

data of the experimental groups if they involved similar interventions according to the protocol. Finally, in cases where outcome data are available for subgroups of preterm infants as part of a larger studied group, only the data from the subgroup that is the closest to our population of interest (ie, preterm infants of less than 29 weeks' gestation) will be included in the combined analyses for this outcome. Any specification about randomisation regarding any subgroup we would select will be extracted.

Risk of bias in individual studies

Risk of bias will be assessed by EP and NMPH, independently and in duplicate, for each of the included studies using the revised Cochrane risk of bias tool (RoB 2.0; https://www.riskofbias.info/welcome/rob-2-0-tool).[34] Any discrepancy will be solved by AB. Supporting information will be documented. The following domains of the risk of bias will be assessed: (1) Risk of bias arising from the randomisation process, (2) Risk of bias due to deviations from the intended interventions, (3) Risk of bias due to missing outcome data, (4) Risk of bias in measurement of the outcome and (5) Risk of bias in selection of the reported result. Judgement will be classified as 'low' or 'high' risk of bias or expressed 'some concerns'. We will also rate the overall risk of bias for each outcomes following guidance for RoB 2.0. The highest risk of bias level in any of the domains assessed will be considered as overall risk of bias for each study.

Summary measures and synthesis of results

Cochrane Review Manager V.5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2012) will be used to present review results. We will report the effect sizes as risk ratios for treatment along with 95% CIs. Pooled and individual estimates and 95% CI will be presented in forest plots. We will perform random effects meta-analysis to combine effect estimates across trials, as we anticipate the trials' population, interventions and methods will not be judged sufficiently similar for fixed-effects models. We will assess between-study heterogeneity of the effect estimates by inspecting the forest plots and calculating τ^2 and I^2 statistics. In cases of notable heterogeneity (I^2>75%), we will consider possible sources. Prespecified subgroup analyses are planned, where possible, for the infant gestational age (less than 27 weeks; 27 weeks or more), sex (male; female), the marine source of DHA (alga oil; fish oil), the mode of administration (direct enteral supplementation to the preterm; supplementation of human milk or formula), the duration of exposure (less than or equal to 1 month; greater than 1 month), the use of intravenous DHA-rich lipids in standard care (yes; no) and the mode of delivery (caesarean; vaginal).

Sensitivity analysis will be performed according to the accuracy of the BPD definition that is, based on a standardised supplemental oxygen reduction test. A sensitivity analysis excluding studies with a high overall risk of bias will also be performed according to the risk of bias of the RCTs assessed using the Cochrane instrument (RoB 2.0).

Publication bias

Publication bias will be assessed by plotting the effect size for each trial against measures of each study's precision. As suggested in the Cochrane handbook, funnel plot assessment will be performed if more than 10 studies are included.[25] If asymmetry in the funnel plot is seen, we will review the characteristics of the trials to assess whether the asymmetry is due to a publication bias or other factors.

Patient and public involvement

Patients or the public were not involved in the design of this protocol. There is no plan to involve patients or the public in the conduct, reporting or dissemination of this research.

Ethics and dissemination

This protocol for a systematic review and meta-analysis does not require ethics approval, as no primary data are collected. Although their physiopathological role on inflammation, pulmonary and cerebral development and growth profile are not yet well understood, omega-3 LCPUFA is largely provided for nutrition care in neonatal units, commercially promoted and widely used by mothers. This review will guide mothers who delivered very preterm infants in the choice to provide DHA supplements or enriched milk for the prevention of BPD. It will also inform healthcare professionals of the potential benefits or harms of high doses of DHA on the risk for BPD. We will communicate the results of the review through conferences, media interviews and publications to peer-review journals.

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Contributors IM contributed to conception and design of the study, developed the criteria and the search strategy and drafted the manuscript. AB, MG, LM and MM contributed to conception and design of the study and developed the criteria. EP contributed to conception and design of the study, developed the criteria and the search strategy. FB developed the search strategy. All authors revised the manuscript for important intellectual content and approved the final manuscript.

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Competing interests IM and MM were both principal investigators of RCTs expected to be included in this review.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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