Omega-3 Long-chain Polyunsaturated Fatty Acids for Bronchopulmonary Dysplasia: A Meta-analysis

Qian Wang, PhD,[a]* Bing Zhou, PhD,[b]* Qiliang Cui, BS,[c] Chao Chen, MD, PhD[a]

abstract

CONTEXT: Previous studies have suggested that intervention with omega-3 long-chain polyunsaturated fatty acids (N-3 LCPUFAs), especially docosahexaenoic acid, can reduce the incidence of bronchopulmonary dysplasia (BPD) in preterm infants. However, conflicting results have been reported.

OBJECTIVE: We conducted this meta-analysis to investigate the effect of intervention with N-3 LCPUFAs on the incidence of BPD in preterm infants.

DATA SOURCES: PubMed, Embase, and the Cochrane Library were searched for articles published from database inception to October 1, 2018.

STUDY SELECTION: We included randomized controlled trials (RCTs) in which the effect of intervention with N-3 LCPUFAs on the incidence of BPD was examined.

DATA EXTRACTION: Two independent authors conducted the literature search and data extraction. The risk ratio was determined, and subgroup analyses were performed.

RESULTS: After applying the inclusion criteria, 14 RCTs with 3531 preterm infants were included in the study. Intervention with N-3 LCPUFAs revealed no significant effect on the incidence of BPD in preterm infants (risk ratio: 0.99; 95% confidence interval: 0.84–1.18; $Z = 0.08$; $P = .93$). Our secondary subgroup analysis, which was stratified by gestational age, birth weight, dosage of docosahexaenoic acid, and duration of intervention, also revealed no significant effects.

LIMITATIONS: The populations, protocols, and pharmaceutical ingredients of N-3 LCPUFAs vary among the included RCTs.

CONCLUSIONS: The results of our meta-analysis indicate that intervention with N-3 LCPUFAs cannot prevent BPD in preterm infants. These findings provide no support for intervention with N-3 LCPUFAs in preterm infants.

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Bronchopulmonary dysplasia (BPD) is 1 of the most serious and common complications in preterm infants, and it is characterized by an inflammatory process that causes abnormal lung development and decreased vascular and alveolar capacities.[1–3] Infants with BPD manifest aberrant pulmonary and cardiovascular development and impaired long-term neurodevelopment.[2] BPD clinically presents with a persistent need for supplemental oxygenation or respiratory support beyond the neonatal period.[4]

Dysregulated inflammation has been shown to play a key role in the pathogenesis of BPD.[1] In addition to promoting the cognitive development of preterm infants,[5–9] omega-3 long-chain polyunsaturated fatty acids (N-3 LCPUFAs), especially docosahexaenoic acid (DHA), have been shown to modulate inflammatory responses.[1,10–14] Studies of experimental models revealed reduced inflammatory responses,[15–17] improved lung growth, and increased production of pulmonary surfactant[18,19] with intervention with N-3 LCPUFAs. Animal studies also revealed decreased inflammatory responses with dietary DHA supplementation in lung injury models induced by lipopolysaccharide intervention or bacterial infection.[20,21] Previous observational data from preterm infants showed an association between a low blood concentration of N-3 LCPUFAs and BPD.[22] Although the mechanisms were not completely understood, the anti-inflammatory properties of N-3 LCPUFAs were thought to include changes in membrane fluidity, the toll-like receptor 4 signaling pathway,[23,24] and the PPARγ[25] signaling pathway. These changes resulted in modified gene transcription or increased production of anti-inflammatory lipid mediators.[26] Researchers conducted studies with transgenic mice that expressed the *fat-1* gene and encoded an N-3 LCPUFA desaturase to produce N-3 LCPUFAs such as DHA.[27] These mice demonstrated a remarkable decrease in inflammatory responses to acute lung inflammation.[28] Therefore, researchers speculated that intervention with N-3 LCPUFAs might be effective for controlling inflammation that predisposed preterm infants to BPD.

In recent years, a series of randomized controlled trials (RCTs) have been conducted to investigate the efficacy of intervention with N-3 LCPUFAs on BPD.[1,9,29–40] However, these RCTs have resulted in heterogeneous outcomes. Although most RCTs revealed no significant effect,[9,29–35,37–40] the Docosahexaenoic Acid for the Improvement of Neurodevelopmental Outcome in Preterm Infants (DINO) trial, which included 657 preterm infants <33 weeks' gestational age (GA), demonstrated that intervention with 1% DHA significantly reduced the risk of BPD compared with intervention with 0.33% DHA.[29,41] A previous meta-analysis of clinical trials from 1996 to 2011, which included the DINO trial, also revealed that intervention with N-3 LCPUFAs reduced the incidence of BPD in preterm infants born at ≤32 weeks' GA.[42] However, the N-3 Fatty Acids for Improvement in Respiratory Outcomes (N3RO) trial (a recent multicenter RCT of 1205 preterm infants <29 weeks' GA conducted at 13 centers in Australia, New Zealand, and Singapore) revealed that preterm infants given DHA showed a greater incidence of BPD.[1] Therefore, we believed that establishing a causal link between intervention with N-3 LCPUFAs and incidence of BPD had important clinical implications for neonatal care. This meta-analysis was performed to investigate the efficacy of intervention with N-3 LCPUFAs on the incidence of BPD.

METHODS

Search Strategy

Two reviewers (Q.W. and B.Z.) conducted a literature search using the following search terms on Embase and the Cochrane Library: (docosahexaenoic acid OR DHA OR long chain polyunsaturated fatty acid OR LCPUFA OR fish oil) AND ("Infant, Extremely Premature" [Mesh] OR "Premature Birth" [Mesh] OR "Infant, Premature" [Mesh]) AND (random* OR "Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]) on PubMed and (long chain polyunsaturated fatty acid OR LCPUFA OR DHA OR docosahexaenoic acid OR fish oil) AND (preterm OR premature) AND (Randomized Controlled Trials OR RCT OR random). Publications from database inception to October 1, 2018, were included without a language restriction. Then all reference citations were pooled, and duplicates were excluded. The bibliographies of the reviewed articles were manually searched for potentially relevant citations that were not detected in the electronic literature search.

Inclusion Criteria

The inclusion criteria of our meta-analysis were as follows: (1) RCTs in which preterm infants (<37 weeks' GA) were assessed, (2) preterm infants given a formula containing N-3 LCPUFAs or given a direct oral dose of N-3 LCPUFAs, (3) intervention commencing within 1 month of birth, and (4) report of an incidence of BPD or oxygen dependency for ≥28 days after birth or ≥36 weeks' postmenstrual age.

Two authors (Q.W. and B.Z.) independently assessed the title, abstract, and full text of each article for eligibility, and in the case of differing opinions, a third author (C.C.) determined final eligibility.

Date Extraction and Synthesis

Data from all the included RCTs were extracted independently by the 2 authors (Q.W. and B.Z.). Details of

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unpublished data were requested via e-mail from the authors. The 2 authors independently assessed the quality of each RCT in accordance with the Modified Jadad Scale[43–47] (≥5 indicated high quality). The extracted data included authors and references, the year of publication, number of participants, GA and birth weight (BW), start and duration of intervention, means of intervention, the Modified Jadad Scale score, and outcome measurements of BPD.

Data Analysis

Review Manager software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to analyze the data. Publication bias was assessed by plotting the effect size against the sample size for each trial (funnel plot).[48] The heterogeneity of the treatments used among the RCTs was assessed visually from the forest plot of mean differences. Statistical estimates of heterogeneity were also assessed by using a Q statistic of the χ^2 test. In addition, the effect of heterogeneity was evaluated with an I^2 statistic. A significant Q statistic ($P < .1$ or $I^2 > 50\%$) indicated differences in RCT characteristics and high heterogeneity. Because of the anticipated heterogeneity from the included RCTs, we calculated summary statistics with a random-effects model. For dichotomous outcomes, the risk ratio (RR), with a 95% confidence interval (CI), was calculated. Our threshold P value for significance was <.05 for the primary analysis and all subgroup analyses.

RESULTS

Study Selection and Characteristics

We obtained 277 studies; 14 RCTs with 3531 participants met our inclusion criteria.[1,9,29–40] A flow diagram depicting our reasons for excluding studies is shown in Fig 1. The characteristics of the included RCTs are shown in Table 1. The DINO trial, which involved 657 participants, demonstrated that a higher dosage of N-3 LCPUFAs significantly reduced the incidence of BPD,[29] whereas the N3RO trial, which involved 1205 participants, reported a negative effect for intervention with DHA on the incidence of BPD.[1] Twelve of the included RCTs revealed that intervention with N-3 LCPUFAs had no effect on the incidence of BPD.[9,30–40] Twelve RCTs were considered high quality by the Modified Jadad Scale score,[1,29–39] and BPD was diagnosed in 13 RCTs by using a specific assessment.[1,9,29–40] The primary outcome was the incidence of BPD in preterm infants in the N-3 LCPUFA intervention and in control groups of the 14 RCTs. Because of the diversity among the included RCTs, we stratified the RCTs into subgroups by GA and BW, dosage of DHA, and duration of intervention.

Efficacy of Intervention With N-3 LCPUFAs on the Incidence of BPD

We found no evidence of publication bias, as depicted in the funnel plot (Fig 2). With our meta-analysis, we failed to identify either a positive or negative significant effect of intervention with N-3 LCPUFAs on the incidence of BPD (RR: 0.99; 95% CI: 0.84–1.18; $Z = 0.08$; $P = .93$). A forest plot was constructed to compare differences in the incidence of BPD between the N-3 LCPUFA intervention and control groups (Fig 3A). We found a modest heterogeneity among the RCTs but no statistical significance ($\chi^2 = 17.89$; degree of freedom = 13; $P = .16$; $I^2 = 27\%$). Furthermore, no significant difference was found when low-quality RCTs were excluded (RR: 1.02; 95% CI: 0.85–1.22; $Z = 0.21$; $P = .83$; Fig 3B). The heterogeneity test showed that the I^2 value was 31%.

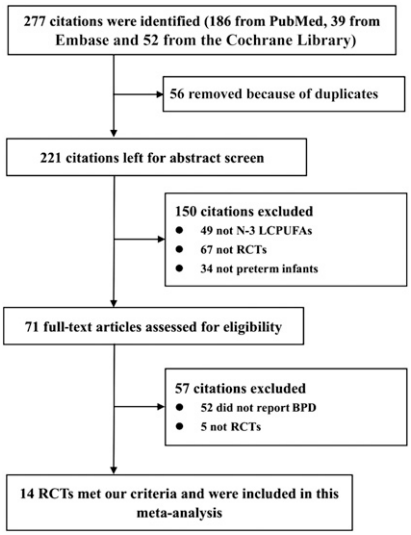

FIGURE 1
Selection of eligible trials. This flow diagram depicts reasons for exclusion of identified citations.

Analyses of the Stratified Subgroups by Participant GA and BW

Analyses of the stratified subgroups revealed no significant effect on preterm infants with a GA of <33 weeks or a BW of <1500 g (RR: 1.00; 95% CI: 0.82–1.21; $Z = 0.04$; $P = .97$; Fig 4A) and preterm infants with a GA of <30 weeks or a BW of <1000 g (RR: 1.08; 95% CI: 0.87–1.35; $Z = 0.72$; $P = .47$; Fig 4B). The heterogeneity tests revealed that I^2 values were 34% and 12%, respectively.

Analyses of the Stratified Subgroups by Dosage of DHA

Analyses of the stratified subgroups revealed no significant effect on preterm infants who received DHA at a dosage of ≤0.33% (RR: 0.96; 95% CI: 0.72–1.29; $Z = 0.26$; $P = .79$; Fig 5A) or at a dosage of >0.33% (RR: 1.19; 95% CI: 0.59–2.43; $Z = 0.49$; $P = .63$; Fig 5B). The heterogeneity tests showed that I^2 values were 16% and 64%, respectively.

Analyses of Stratified Subgroups by Duration of Intervention

Analyses of the stratified subgroups revealed no significant effect on preterm infants who received N-3 LCPUFAs for ≤1 month (RR: 1.10; 95% CI: 0.63–1.93; $Z = 0.33$; $P = .74$; Fig 6A), for >1 month (RR: 0.99; 95%

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TABLE 1 Characteristics of Included RCTs

Author and Publication Year	Participants (Intervention Group/Control Group)	Inclusion Criteria, GA/BW	Start of Intervention (After Birth)	Duration of Intervention/Means of Intervention	Modified Jadad Score (Total)	Outcome Measurement of BPD
Collins et al[1] 2017	1205 (592/613)	<29 wk, commenced enteral feeding in the previous 3 d/NR	As soon as possible	Until 36 wk postmenstrual age or discharge from the hospital/enteral	2/2/2/1 (7)	Requirement for supplemental oxygen and/or assisted ventilation at 36 wk postmenstrual age
Baack et al[9] 2016	60 (31/29)	24–34 wk/NR	Within the first week of life	Until discharge or term/enteral	1/1/2/0 (4)	NR
Robinson et al[33] 2016	28 (9/9/10)[a]	<34 wk/<1000 g	Within 72 h	8 wk/enteral	2/1/2/0 (5)	Oxygen requirement at 36 wk postmenstrual age
Skouroliakou et al[34] 2016	51 (25/26)	26–32 wk/NR	As soon as possible	Up to d 30/parenteral	2/1/2/1 (6)	Need for oxygen for at least 28 d
D'Ascenzo et al[35] 2014	80 (39/41)	NR/500–1249 g	Within the first hour of life	18 d/parenteral	1/2/2/0 (5)	Requiring mechanical ventilation, CPAP, or supplemental oxygen concentration ≥30% and oxygen saturation between 90% and 96% at 35–37 wk postmenstrual age
Moltu et al[36] 2014	44 (23/21)	NR/<1500 g	<24 h of life	Until discharge/enteral	2/2/1/1 (6)	Oxygen dependency at 36 wk postmenstrual age
Beken et al[37] 2014	80 (40/40)	<32 wk/<1500 g	Within the first day of life	Until corrected age of 32 wk or postnatal 28th d/parenteral	1/2/2/1 (6)	Oxygen dependency beyond 36 wk corrected age
Manley et al[29] 2011 or Makrides et al[41] 2009	657 (322/335)	<33 wk postmenstrual age/NR	Within 2–4 d	9–10 wk/enteral	2/2/2/1 (7)	Requiring oxygen at 36 wk
Groh-Wargo et al[38] 2005	57 (18/18/21)[b]	≤35 wk postmenstrual age/NR	Within 10 d	14.5 mo/enteral	2/1/2/0 (5)	Requiring oxygen at 36 wk postmenstrual age with severe or chronic changes to the lungs as seen on chest radiographs
Clandinin et al[30] 2005	361 (112/130/119)[c]	23–36 wk/<2500 g	Within 72 h of first enteral feeding	By d 28/enteral	2/1/2/0 (5)	Need for supplemental oxygen beyond 1 mo postnatal age or 36 wk corrected age
Fewtrell et al[31] 2004	238 (122/116)	<35 wk postmenstrual age/≤2000 g	Within the first day of life	Until 9 mo after term/enteral	2/1/2/0 (5)	Respiratory assistance (ventilation, CPAP, or supplemental oxygen) at 36 wk
Fewtrell et al[39] 2002	195 (95/100)	<37 wk postmenstrual age/<1750 g	Within 5 d	1 mo/enteral	1/2/2/1 (6)	Oxygen requirement >30% for >28 d
O'Connor et al[32] 2001	427 (140/143/144)[b]	<33 wk postmenstrual age/750–1805 g	Within 3 d	14 mo/enteral	2/1/2/0 (5)	Supplemental oxygen beyond 1 mo postnatal age or at 36 wk postmenstrual age
Carlson et al[40] 1996	59 (26/33)	<30 wk/NR	Between d 2 and 5 of life	Until discharge/NR	1/1/1/0 (3)	Supplemented oxygen for 28 d and/or pulmonary changes on radiologic examination

CPAP, continuous positive airway pressure; NR, not recorded.

[a] Low-dose DHA group/high-dose DHA group/placebo without DHA.

[b] (Fish/fungal oil group)/(egg-derived triglyceride /fish oil group)/control group.

[c] Algal-DHA supplement/fish-DHA supplement/control group.

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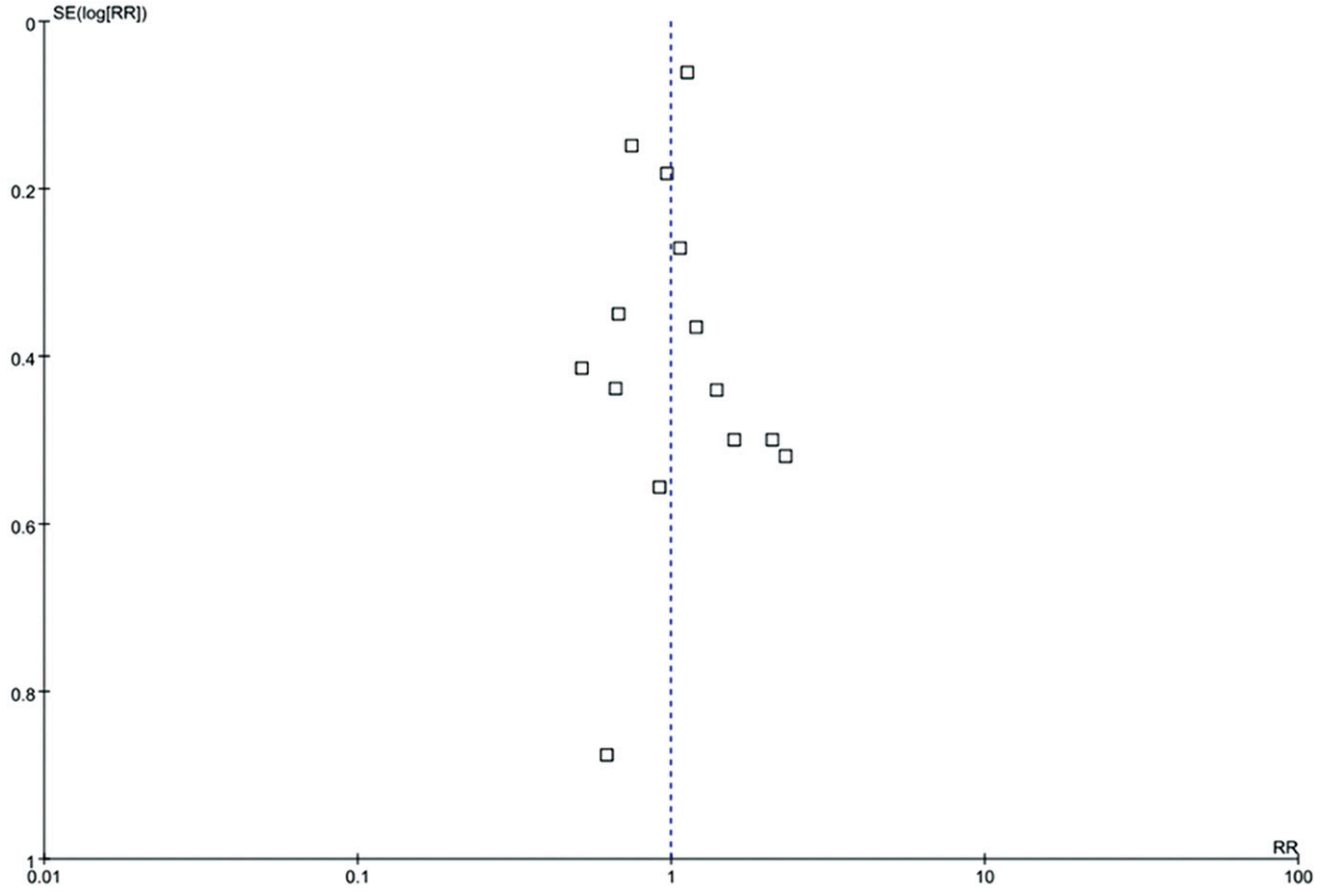

FIGURE 2
Funnel plot used to evaluate publication bias.

CI: 0.82–1.19; Z = 0.14; P = .89; Fig 6B), or for ≥2 months (RR: 0.92; 95% CI: 0.74–1.14; Z = 0.79; P = .43; Fig 6C). The heterogeneity tests revealed that I^2 values were 53%, 35%, and 7%, respectively.

DISCUSSION

BPD remains 1 of the most serious complications that occurs in 45% of infants born at <29 weeks' GA.[4,49] Sustained oxidative stress and dysregulated inflammation are known to be the underlying pathogenesis of the development of BPD.[50,51] N-3 LCPUFAs, especially DHA, are crucial for the integrity of cell membranes in the retina and cerebral cortex[52–54] and have been considered to play an important role in promoting neurodevelopment.[5,6,30,32,41,55–58] Guided by short-term benefits for development, researchers have recommended use of formula with a proportion of DHA of between 0.2% and 0.33% of the total quantity of fatty acids for neurodevelopment.[59] The placenta provides the fetus with N-3 LCPUFAs, especially DHA, during the last trimester of pregnancy.[60–62] During this time, DHA is transferred at a rate 3 times higher than that of arachidonic acid and at rates 1.3 and 1.6 times higher than those of α-linolenic acid and linoleic acid, respectively.[63,64] Researchers also have indicated that the relative proportions of DHA are lower in preterm infants than in term infants,[63,64] and such patients exhibit limited ability to counteract inflammatory and oxidative stress during the neonatal period.[64–67] Because of the anti-inflammatory properties of N-3 LCPUFAs, researchers have conducted clinical studies and RCTs to investigate whether intervention with N-3 LCPUFAs can reduce the incidence of BPD.

In our meta-analysis, which included 14 RCTs, we failed to find any significant effect. We were aware that the quality of the meta-analysis depended on the quality of the included RCTs. Consequently, we scrutinized the selected RCTs by using the Modified Jadad Scale, a strict quality-assessment criterion.[43–47] However, we were still unable to find any significant effect after low-quality RCTs were excluded.

Because extremely preterm infants had a N-3 LCPUFA deficiency,[63,64] we stratified RCTs to investigate the efficacy in preterm infants with a GA

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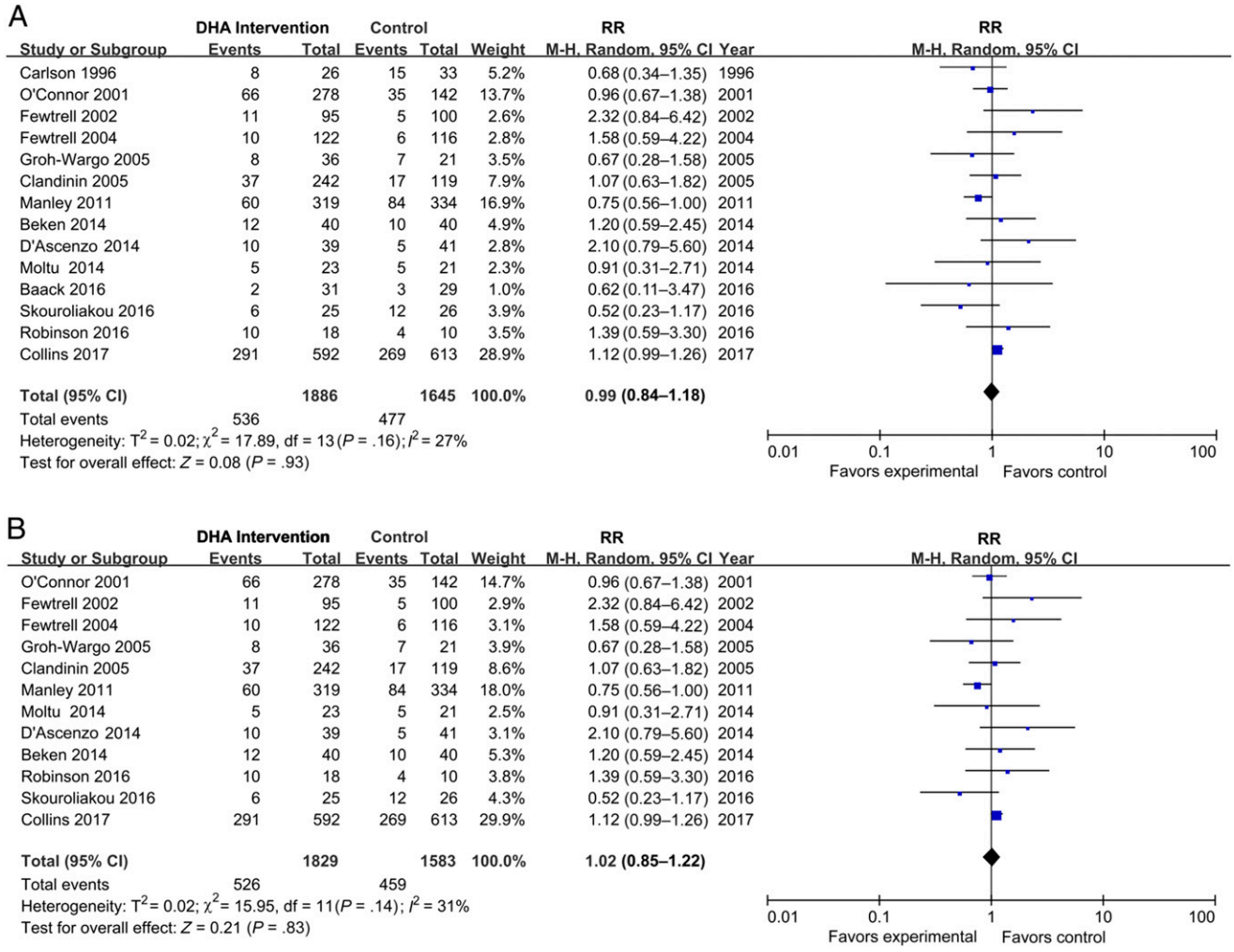

FIGURE 3

A, Effect of N-3 LCPUFA intervention on BPD. B, Forest plots of high-quality RCTs considered by the Modified Jadad Scale. df, degree of freedom; M-H, Mantel-Haenszel.

of <33 weeks or a BW of <1500 g and in preterm infants with a GA of <30 weeks or a BW of <1000 g. Unlike in previous meta-analyses,[42] we did not find a significant effect (Fig 4). We noticed that the authors of a previous work recommended intervention with DHA for preterm infants at a proportion of 0.2% to 0.33% of the total fatty acid content. Moreover, a dosage of 0.33% DHA was approximate to the breast milk concentration.[59] We stratified RCTs by the dosage of DHA used (≤0.33% and >0.33%), but no significant effect was detected (Fig 5). We also considered whether the duration of the intervention would influence the efficacy of N-3 LCPUFAs. Thus, we stratified the RCTs by duration of the intervention (≤1 month, >1 month,/ and ≥2 months), but no significant effect was found (Fig 6).

A previous meta-analysis of 12 clinical trials (RCTs and observational studies) reported that intervention with N-3 LCPUFAs reduced the incidence of BPD in preterm infants born at ≤32 weeks' GA.[42] However, with our meta-analysis, we provide strong evidence that intervention with N-3 LCPUFAs cannot prevent BPD in preterm infants. Furthermore, we cannot neglect the fact that a larger sample size will lead to a greater statistical power in the combined results. The previous meta-analysis was published in 2014 and included clinical trials from database inception to 2011. The statistical power of the DINO trial could affect the combined results of preterm infants ≤32 weeks' GA.[29,42] However, because the N3RO trial and the other 5 RCTs included in this research included >100 participants[1,29–32,39,41] and because 7 of the included RCTs were published after 2011,[1,9,33–37] the DINO trial no longer had the statistical power. With the exception of the DINO and N3RO trials, most included RCTs did not reveal a significant effect of intervention

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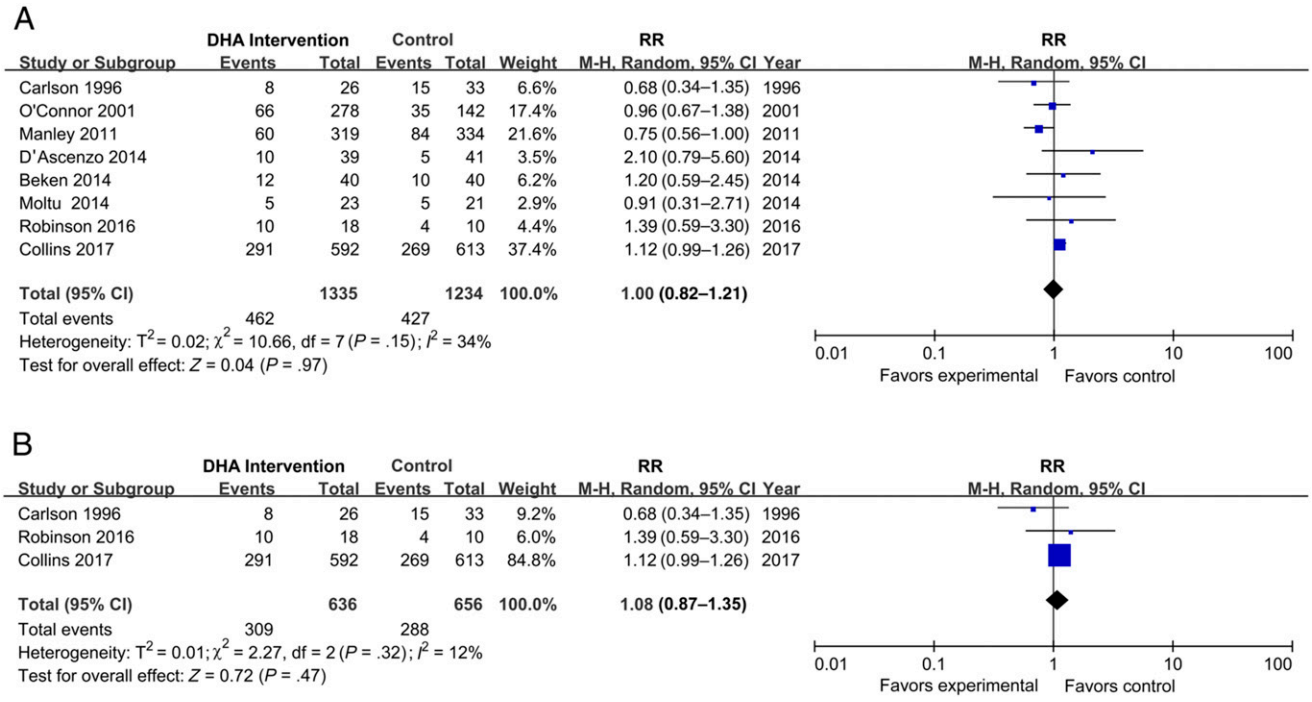

FIGURE 4

Stratified subgroup analyses used to investigate the effects of N-3 LCPUFAs on preterm infants. A, GA of <33 weeks or BW of <1500 g. B, GA of <30 weeks or BW of <1000 g. df, degree of freedom; M-H, Mantel-Haenszel.

with N-3 LCPUFAs on the incidence of BPD in preterm infants. Therefore, we believe that intervention with N-3 LCPUFAs is not able to reduce the incidence of BPD in preterm infants. By contrast, the existing evidence is not enough to prove that intervention with N-3 LCPUFAs results in a greater incidence of BPD in preterm infants.

The main limitation of the present meta-analysis is the heterogeneity of the populations, protocols, and pharmaceutical ingredients of N-3 LCPUFAs among the included RCTs.

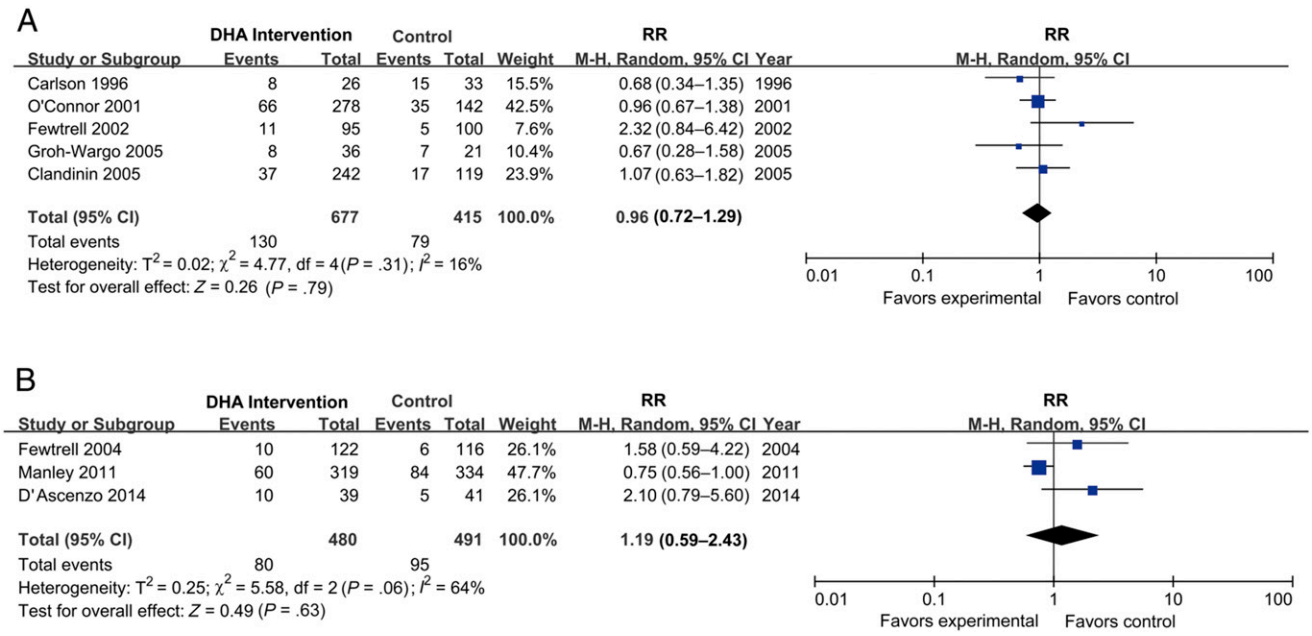

FIGURE 5

Stratified subgroup analyses used to investigate the effects of dosage of DHA. A, Less than or equal to 0.33% of total fatty acids. B, Greater than 0.33% of total fatty acids. df, degree of freedom; M-H, Mantel-Haenszel.

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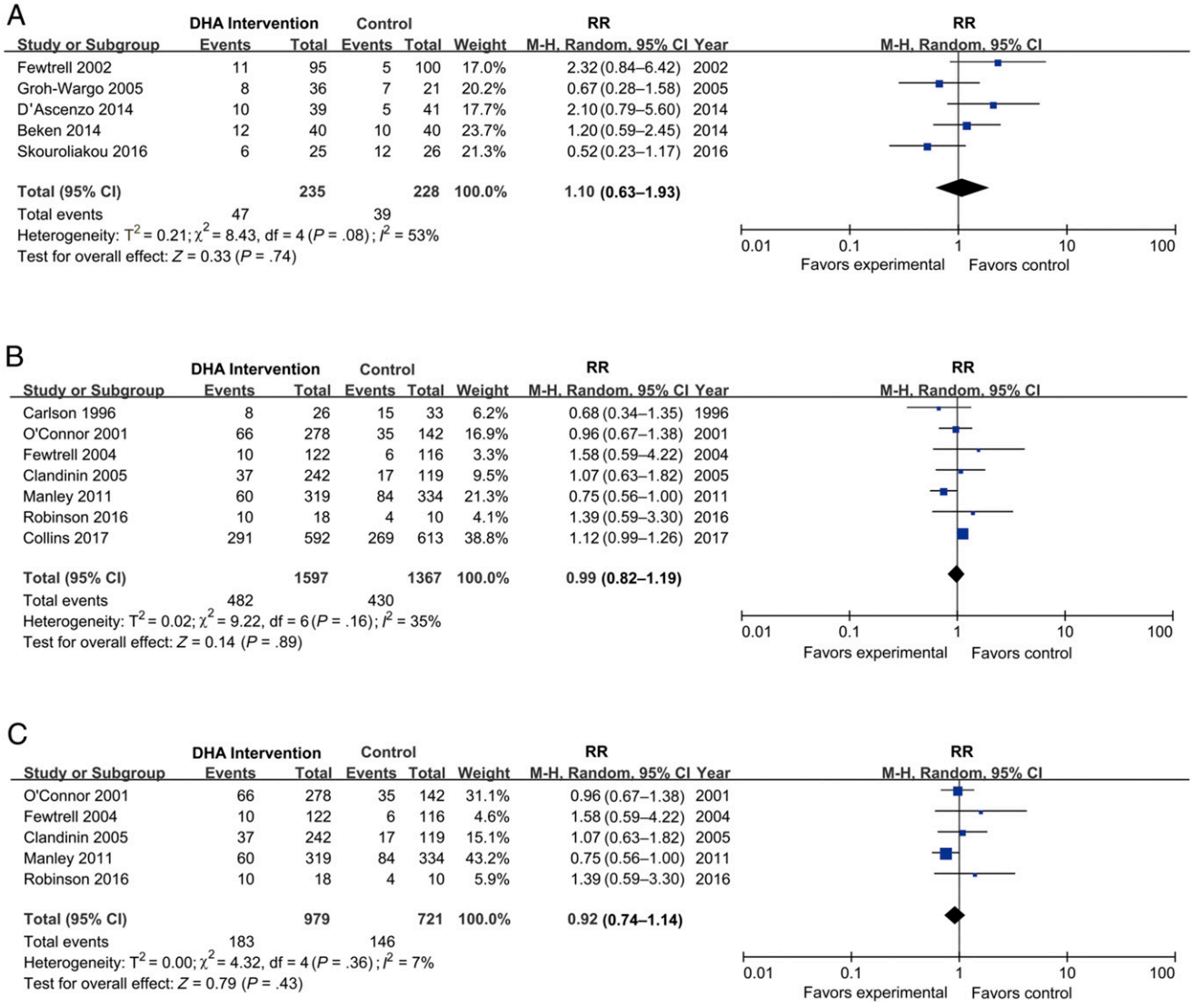

FIGURE 6

Stratified subgroup analyses used to investigate the effects of intervened duration. A, Less than or equal to 1 month. B, Greater than 1 month. C, Greater than or equal to 2 months. df, degree of freedom; M-H, Mantel-Haenszel.

We believe that these heterogeneous results can be attributable to several factors. First, the heterogeneity is substantial among the included RCTs in terms of ethnicities and populations, intervention protocols, and outcome measurements. Furthermore, the primary outcomes of most included RCTs are not respiratory outcomes. Second, the RCTs included in our meta-analysis were published between 1996 and 2017, during which time the intrinsic incidence and mortality of BPD varied because of advancements in treatment, respiratory support technology, and nutritional supplementation. Third, the incidence of BPD is associated with both GA and BW, and the RCTs included in our meta-analysis included preterm infants from 24 to 37 weeks' GA. In fact, the incidence of BPD in each of the included RCTs varied widely, with an incidence as low as 5% reported in some trials[9] and an incidence as high as 50% reported in some trials.[1,33]

In addition to respiratory outcomes, the results of the interventions with N-3 LCPUFAs or DHA varied widely. It was recently reported that in an RCT conducted in 9 NICUs, intervention with DHA did not reveal beneficial effects on the Bayley Scales of Infant Development, Third Edition cognitive score, and it had a small to medium negative effect on Bayley Scales of Infant Development, Third Edition language scores and on the effortful control scores of the Early Childhood Behavior Questionnaire,[68] although it had been proven in previous RCTs and meta-analyses that intervention with N-3 LCPUFAs promoted neurodevelopment in preterm infants.[5,6,30,31,41] Another recent RCT also revealed that supplementation

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with omega-3 fatty acids did not result in a lower incidence of major cardiovascular events compared with a placebo.[69] A meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events and provided no supporting evidence for current recommendations to use such supplements in people with a history of coronary heart disease,[70] which was in contrast with findings of previous researches. We also noticed that excessive DHA supplementation (8–50 the amount used in control groups) impeded neurodevelopment and increased mortality.[71–73] We believe that the results of our meta-analysis have provided strong evidence that intervention with N-3 LCPUFAs cannot prevent BPD in preterm infants. Therefore, we are concerned about the recommendation of daily N-3 LCPUFA supplementation, until appropriate administration and pharmaceutical ingredients of intervention with N-3 LCPUFAs are established, because the efficacy of such intervention seems unreliable and variable.

CONCLUSIONS

Our meta-analysis reveals that intervention with N-3 LCPUFAs cannot prevent BPD in preterm infants. Findings of the current meta-analysis and recent research studies provide no supporting evidence for current recommendations to administer intervention with N-3 LCPUFAs routinely. A future update with long-term follow-up data is needed, and further investigations and larger-scale RCTs are required to implement specific stratifications to investigate whether the efficacy of N-3 LCPUFAs is affected by populations, protocols, and the specific pharmaceutical ingredients of N-3 LCPUFAs.

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
BW: birth weight
CI: confidence interval
DHA: docosahexaenoic acid
DINO: Docosahexaenoic Acid for the Improvement of Neurodevelopmental Outcome in Preterm Infants
N-3 LCPUFA: omega-3 long-chain polyunsaturated fatty acid
N3RO: N-3 Fatty Acids for Improvement in Respiratory Outcomes
RCT: randomized controlled trials
RR: risk ratio

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