Effect of long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment: a systematic review of randomized controlled trials¹–³

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ABSTRACT
Background: Supplementation of preterm formulas with long-chain polyunsaturated fatty acids (LCPUFAs) is based on their effectiveness to increase blood status and improve visual outcomes. Dispute remains over their efficacy on global development.

Objective: The objective was to compare the effects of LCPUFA-supplemented with those of control formulas on neurodevelopment and diseases associated with prematurity.

Design: We systematically reviewed randomized controlled trials involving preterm infants that tested LCPUFA-supplemented formulas. The weighted mean differences (WMDs) in neurodevelopmental scores and relative risk (RR) of disease were calculated to compare infants fed LCPUFA-supplemented formula with those fed control formula.

Results: No clear differences in Bayley Scales of Infant Development (BSID) scores were observed between groups. Mental development of LCPUFA-supplemented infants was 3.4 points higher than that of control infants with BSID version II (WMD: 3.44; 95% CI: 0.56, 6.31; P = 0.02; n = 879), although it was driven by 2 trials with large effect sizes and wide CIs. Psychomotor development was lower in supplemented infants tested with BSID version I (WMD: −7.99; 95% CI: −14.00, −1.99; P = 0.009; n = 87); however, it was limited by small sample sizes. No differences in the RR of sepsis (1.08; 95% CI: 0.79, 1.46; P = 0.63; n = 1333) or in the RR of necrotizing enterocolitis (1.13; 95% CI: 0.62, 2.04; P = 0.69; n = 1333) were found. Similarly, the risks of retinopathy of prematurity, intraventricular hemorrhage, and bronchopulmonary dysplasia were not different between groups, but data were limited by small sample sizes and trials with an increased risk of bias.

Conclusions: LCPUFA-supplemented formula does not alter the risk of NEC or sepsis. Further work is needed to determine the extent of benefit of LCPUFA-supplemented formula on the mental development of preterm infants.

INTRODUCTION

Preterm infants exhibit poorer performance in multiple developmental domains, including cognition, language processing and behavior, and differences in brain volume and composition, than do infants born full term (1–6). Long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexaenoic acid (DHA, 22:6n–3) and arachidonic acid (AA, 20:4n–6) are rapidly accumulated into neural tissues during the last trimester of gestation and early postnatal life. Biochemical studies have shown that term infants, who receive a full complement of all LCPUFAs through breast milk, have higher concentrations of LCPUFAs in their blood cells and higher concentrations of DHA in the brain than do infants fed formulas that do not contain LCPUFAs (7).

Several randomized controlled trials (RCTs) have reported that preterm infants fed LCPUFA-enriched formulas have enhanced visual development, including improved retinal sensitivity and visual acuity, compared with those fed unsupplemented formulas (8–12). Although an increasing number of trials have investigated whether formulas supplemented with LCPUFAs have the potential to improve the neurodevelopment of preterm infants over the longer term, most have not had sufficient sample sizes to make robust conclusions.

LCPUFAs have bioactive properties that modulate physiological functions. In high doses, n–3 LCPUFAs increase bleeding times (13–15) and alter immune responses in adults and infants (16, 17). The 2 families of LCPUFAs added to infant formulas (largely as DHA and AA) appear to have differential effects on inflammatory immune responses in adults. An increase in dietary n–6 fatty acids tends to promote, whereas n–3 LCPUFAs tend to dampen, inflammatory responses (16). It is therefore possible that LCPUFA-supplemented formulas have the potential to modulate diseases with a vascular or immune component. Many trials have reported the incidence of diseases associated with prematurity, such as retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and neonatal sepsis. However, there

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has been no formal synthesis of the effects of LCPUFA-supplemented formula on the prevalence of these diseases in preterm infants.

Our aim was to evaluate the effect of feeding LCPUFA-enriched compared with control formula to preterm infants on neurodevelopment and on the risk of NEC, sepsis, ROP, IVH, and BPD through a systematic review and meta-analysis of published RCTs. We focused on these outcomes because they are associated with the long-term health and well-being of infants born preterm (3, 18–20).

**METHODS**

**Search strategy**

Both the MEDLINE and EMBASE databases were searched for relevant articles using the search terms *preterm*, *long-chain polyunsaturated fatty acids*, *fatty acid*, and *n−3 fatty acid*; the search was limited to studies in humans. No language restriction was applied. Reference lists of eligible articles identified from this search were checked to reveal other potentially relevant trials. The last search was performed on 24 January 2007.

**Selection**

RCTs involving preterm infants born <37 wk of gestation that compared infants fed a standard preterm formula containing no LCPUFAs with those fed a formula containing n−3 LCPUFAs or n−3 and n−6 LCPUFAs for ≥1 mo were eligible for inclusion. Articles must have reported at least one of the outcomes of interest, eg, neurodevelopmental assessment (performed with age-standardized, clinically relevant techniques), sepsis, NEC, BPD, ROP, or IVH.

**Data abstraction, synthesis, and analysis**

Double-entry data abstraction was performed by one investigator (LGS). We contacted authors of eligible trials for missing information. Neurodevelopment in all included trials was assessed with version I or II of the Bayley Scales of Infant Development (BSID-I or BSID-II). Because the different versions of the BSID involve different procedures for administration and scoring, the data generated from these tests were considered as separate subgroups in the meta-analysis. Data collected at 12 and 18 mo corrected age were combined within each subgroup because the BSID are standardized for infant age. The neurodevelopmental data from 2 trials with multiple treatment groups were interpolated (12, 21). The mean difference in mental development (MDI) and psychomotor development index (PDI) scores of preterm infants fed standard compared with LCPUFA-supplemented formula were computed in the Review Manager program (RevMan version 4.2, 2003; Cochrane Collaboration) with the use of fixed- or random-effects models. Random-effects models were applied when there was moderate-to-high heterogeneity (indicated by $\chi^2 > 50\%$ and $P < 0.1$). The mean difference in MDI and PDI was weighted according to the sample size and SD of each trial, as determined by the RevMan program.

The relative risk (RR) of NEC, sepsis, ROP, IVH, and BPD in preterm infants fed control compared with LCPUFA-supplemented formula were determined by using fixed- or random-effects models; the random-effects model was applied when heterogeneity was moderate to high (RevMan version 4.2). The RevMan software weighted analyses according to the Mantel-Haenszel technique (22). Analyses were also performed on severe ROP and IVH (grade ≥ 3), because more severe disease is associated with long-term morbidity. An RR of 0 to 0.9 indicates that there is a lower risk in infants fed LCPUFA-supplemented formula relative to control formula, whereas an RR > 1.0 indicates that the LCPUFA-supplemented formula is associated with an increase in risk of disease. No formal assessment of publication bias was performed.

**Validity assessments**

The clinical signs and symptoms applied to diagnose a disease may differ between neonatal units and are subject to change with improvements in clinical practice over time. We addressed these potential differences by performing separate analyses of trials that reported the diseases according to the following definitions: sepsis (confirmed by isolation of a pathogenic microorganism), NEC (confirmed by radiology, surgery, or postmortem examination), BPD (defined as the requirement for oxygen therapy at 36 wk postmenstrual age), and ROP and IVH (diagnosed according to internationally accepted definitions; 23–25). Sensitivity analyses that included trials reporting adequate concealment of allocation and data analysis according to intention-to-treat principles were also performed to evaluate the effect of LCPUFA-supplemented formula in trials with low risk of bias (high methodologic quality).

**RESULTS**

Thirty-two potentially relevant trials were identified by our search strategy (Figure 1). Eighteen trials were excluded because they did not report any of the outcomes of interest (9, 11, 26–41), 2 because they were not randomized trials (42, 43), and 1 because the intervention was only 3 wk (44). One study was also excluded (45) because the clinical data from a proportion of the cohort were reported in a separate larger trial that was already included in the analysis (12). Data from 10 trials were included in the review (12, 21, 46–53).

**Summary of included studies**

The trials included are summarized in Table 1. Seven trials reported global development with the BSID (12, 21, 46, 48–51). NEC was reported in 6 trials (12, 21, 48, 49, 52, 53) and sepsis in 7 trials (12, 21, 47–49, 52, 53). Of the 5 trials that reported BPD outcomes (12, 21, 47, 48, 53), only 1 reported a diagnosis of BPD according to the contemporary definition, ie, the requirement for oxygen at 36 wk postmenstrual age (21). Fewer data were available to investigate the influence of formula supplemented with LCPUFAs on incidences of ROP and IVH. ROP was reported in 3 trials (21, 48, 53), 1 of which categorized ROP by severity (53). IVH was reported in 4 trials (21, 47–49), 2 of which categorized severity (48, 49).

The interventions of all included trials used a standard cow milk–based formula for preterm infants. LCPUFAs were sourced from fish oils, egg triacylglycerol or phospholipids, and algal and fungal oils. All trials included ≥0.2% total fatty acids as n−3 LCPUFAs, and 7 of the 10 trials tested n−6 as well as n−3 LCPUFAs in formulas. Doses of n−3 LCPUFAs ranged from 0.2% to 0.6% of total fatty acids and of n−6 LCPUFAs ranged from 0% to 0.7% of total fatty acids. The supplementation periods varied from 1 mo to >1 y. When intervention periods extended beyond the neonatal period, infants were usually fed a...
transitional or term formula. Three trials permitted breast-milk feeding in addition to the allocated trial formula (12, 21, 49). Participant characteristics differed between trials; some trials included relatively healthy infants born at <37 wk of gestation (48), whereas others included extremely low-birth-weight infants with concomitant morbidities typical of preterm infants (12). Attrition varied between 11% and 50%. The high attrition rate in some trials was due to designs that excluded participants after randomization because of illness or not meeting minimum criteria for formula feeding, which makes it impossible to analyze by intention-to-treat. For example, in one trial, randomized participants were not followed up if they were not exclusively fed trial formula at their expected due date or received ≤80% of the trial formula while hospitalized (21), whereas in another trial they were excluded if they developed neurological abnormalities (51). This is likely to have contributed to the loss to follow-up rates of 24% and 50% in these 2 trials, respectively. Only 2 trials met the criteria for inclusion in sensitivity analyses (48, 49).

Neurodevelopmental outcome

In both mental and motor development indexes, moderate heterogeneity was noted and the primary analyses were computed by using random-effect models. Infants fed LCPUFA-supplemented formula and tested with the BSID-II had an MDI that was 3 points higher than that for infants fed control formula (WMD: 3.44; 95% CI: 0.56, 6.31; n = 879; P = 0.02) (Figure 2A). Fewer MDI data were available for infants tested with BSID-I, and the control and treatment groups did not differ (WMD: –4.09; 95% CI: –9.85, 1.67; n = 97; P = 0.16). Overall, no significant difference in MDI was observed between infants fed control or LCPUFA-supplemented formula when MDI data from both BSID-I and BSID-II assessments were combined (WMD: 2.13; 95% CI: –0.87, 5.14; n = 976; P = 0.16).

Meta-analysis of PDI scores showed no differences between the control and LCPUFA-supplemented groups when tested with the BSID-II (WMD: 2.87; 95% CI: –0.90, 6.65; n = 878; P = 0.14) (Figure 2B). Infants fed LCPUFA-supplemented formula and tested with BSID-I had motor development scores 8 points lower than those of the control group (WMD: –7.99; 95% CI: –14.00, –1.99; n = 87; P = 0.009). No overall differences in PDI were found when all BSID data were combined (WMD: 0.70; 95% CI: –3.26, 4.66; n = 965; P = 0.73).

In sensitivity analyses, there were no clear differences between the LCPUFA-supplemented or control groups in a fixed effects analysis for either mental development (WMD: 1.92; 95% CI: –1.21, 5.06; n = 349; P = 0.2; test for heterogeneity: \( I^2 = 92\% \), \( P = 0.71 \)) or psychomotor development (WMD: 0.06; 95% CI: –2.91, 3.03; n = 349; P = 0.97; test for heterogeneity: \( I^2 = 12.8\% \), \( P = 0.28 \)), although these analyses are restricted by small sample sizes.

Diseases associated with prematurity

The RR of sepsis did not differ between infants fed LCPUFA-supplemented or control formula when all available data were

**FIGURE 1.** Progress of randomized controlled trials (RCTs) determined by a systematic review and meta-analysis that investigated long-chain polyunsaturated fatty acid supplementation of formula for preterm infants.
included (12, 21, 47–49, 52, 53) (Figure 3A) (fixed-effects RR: 1.09; 95% CI: 0.81, 1.48; n = 1519; P = 0.57). This was consistent with the analysis including trials that reported sepsis proven by isolation of the pathogenic organism (12, 21, 48, 49, 53) (Figure 3B) (fixed-effects RR: 1.08; 95% CI: 0.79, 1.46; n = 1333; P = 0.63) and with sensitivity analysis (48, 49) (fixed effects RR: 1.06; 95% CI: 0.53, 2.09; n = 433; P = 0.88; test for heterogeneity: $I^2 = 0\%$, $P = 0.44$; forest plot not shown). Similarly, the risk of NEC did not differ between the LCPUFA-supplemented and control groups when all available data were included (12, 21, 48, 49, 52, 53) (RR: 1.12; 95% CI: 0.64, 1.97; n = 1488; $P = 0.69$; Figure 4A), when NEC was confirmed (12, 21, 48, 49, 53) (RR: 1.13; 95% CI: 0.62, 2.04; n = 1333; $P = 0.69$; Figure 4B), or in sensitivity analysis (48, 49) (RR: 2.50; 95% CI: 0.80, 7.85; n = 433; P = 0.12; test for heterogeneity: $I^2 = 0\%$, $P = 0.93$; forest plot not shown).

There were no clear differences in ROP, IVH, or BPD between preterm infants fed control or LCPUFA-supplemented formula in overall analyses, when trials reported diseases according to the prespecified definitions, or in sensitivity analysis (Table 2). However, in many cases these analyses were limited by the small numbers of infants and low disease rates.

## DISCUSSION

The finding that the effects of dietary LCPUFAs on the mental development of preterm infants varied according to whether BSID-I or BSID-II were used was surprising. Trials using BSID-I tended to report poorer mental development, whereas trials using BSID-II tended to report enhanced mental development with LCPUFA supplementation compared with control. Although psychometric studies have indicated that children tested with the BSID-II have lower mental development scores than do children tested with BSID-I, the scores are generally in the same direction and there is a high correlation between the 2 tests (54–56). Although many elements in BSID-I were retained in BSID-II, the mental scale of BSID-II was revised to include more items that test language and problem solving in the age group 12–18 mo. This, coupled with changes to the administration and scoring of the test, may have introduced systematic differences in the evaluation of the underlying cognitive domains (57). In our meta-analyses, the incongruence observed between the mental development score and version of the BSID added to the heterogeneity between trials and contributed to the need to apply random-effects models. It

### TABLE 1

Summary of randomized clinical trials (RCTs) included in the meta-analysis

<table>
<thead>
<tr>
<th>Author and reference</th>
<th>Participants</th>
<th>Concentration and source of formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor et al, 2001 (12)</td>
<td>427 infants with birth weight &lt;1800 g</td>
<td>Control group: no LCPUFAs</td>
</tr>
<tr>
<td>van Wezel-Meijler et al, 2002 (51)</td>
<td>42 infants born &lt;34 wk gestation, &lt;1750 g, and normal neurological examination</td>
<td>Treatment group: DHA: 0.27% to term, then 0.16%; EPA: 0.08% to term in fish oil formula, then ND in postterm formula. ND in egg TG formulas; DPA: NR; AA: 0.43% to term, then 0.43% Source: egg TG, fish, and fungal oils</td>
</tr>
<tr>
<td>Fewtrell et al, 2002 (48)</td>
<td>195 infants born &lt;37 wk gestation, &lt;1750 g, and FF at day 10</td>
<td>Control group: no LCPUFAs</td>
</tr>
<tr>
<td>Fewtrell et al, 2004 (49)</td>
<td>238 infants born &lt;35 wk gestation, &lt;2000 g</td>
<td>Treatment group: DHA: 0.17%; EPA: 0.04%; DPA: NR; AA: 0.31% Source: egg PL</td>
</tr>
<tr>
<td>Clandinin et al, 2005 (21)</td>
<td>361 infants born &lt;35 wk gestation</td>
<td>Control group: no LCPUFAs</td>
</tr>
<tr>
<td>Fang et al, 2005 (50)</td>
<td>28 infants born 30–37 wk gestation</td>
<td>Treatment group: DHA: 0.32%; EPA: 0.1% in formula supplemented with fish oil; DPA: NR; AA: 0.64–0.67% Source: algal or fish and fungal oils</td>
</tr>
<tr>
<td>Vanderhoof et al, 1999 (52)</td>
<td>155 infants born 750–2000 g (AGA)</td>
<td>Control group: no LCPUFAs</td>
</tr>
<tr>
<td>Carlson, 1992 (46)</td>
<td>79 infants born &lt;1400 g with EI &gt;110 mL·kg⁻¹·d⁻¹</td>
<td>Treatment group: DHA: 0.35%; EPA: NR; DPA: NR; AA: 0.5% Source: algal and fungal oils</td>
</tr>
<tr>
<td>Carlson et al, 1998 (53)</td>
<td>120 infants ≤32 wk gestation (AGA)</td>
<td>Control group: no LCPUFAs</td>
</tr>
<tr>
<td>Foreman-van Drongelen et al, 1996 (47)</td>
<td>43 infants born &lt;37 wk gestation, &lt;1800 g (AGA)</td>
<td>Treatment group: DHA: 0.13%; EPA: ND; DPA: 0.07%; AA: 0.41% Source: egg phospholipids</td>
</tr>
</tbody>
</table>

(Continued; additional data columns shown on next page)
was not possible to combine the BSID-I and BSID-II data in a meaningful way because the differences between trials contributed to a greater diversity in responses than expected. The differences between trials may arise because of the sample population studied, the way the intervention was applied, the types of outcomes, or trial methodology. We have limited confidence in the BSID-I outcome because these data were generated from 2 trials with small sample sizes and methodologic limitations (46, 51).

Whereas the meta-analysis indicated that there was a benefit of LCPUFA supplementation on mental development when the BSID-II test was used, we are concerned about 2 issues. First the effect is driven by 2 trials with large effect sizes. Second, close examination of the forest plot (Figure 2A) shows that the 95% CIs for these 2 trials are 2–3 times wider than those for the other trials (21, 50). Although it could be argued that the developmental advantage observed in these trials may have been due to the use of LCPUFAs in formula at the common ratio of 1:2 (DHA:AA), these data are not supported by other trials that also tested formula at this ratio (12, 48, 51). In addition, most trials included in the meta-analysis had some methodologic limitation that could not exclude the possibility of bias or random error. Thus, despite the intense interest in the role of LCPUFAs on the neurodevelopmental outcomes of preterm infants and their universal addition to preterm infant formulas, the available data from RCTs do not show a robust benefit of LCPUFAs on a global assessment of mental development in the period between 12 and 18 mo corrected age.

Similarly there were no clear differences in psychomotor development with LCPUFA supplementation, although preterm infants fed LCPUFA-supplemented formulas had lower motor development when assessed with BSID-I than did the control

<table>
<thead>
<tr>
<th>Author and reference</th>
<th>Intervention period</th>
<th>Neurodevelopment data</th>
<th>Clinical data</th>
<th>Concealed allocation</th>
<th>ITT analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor et al, 2001 (12)</td>
<td>Day 4 of EI to 12 mo CA</td>
<td>BSID version II at 12 mo CA</td>
<td>NEC, sepsis, BPD</td>
<td>Adequate</td>
<td>No</td>
</tr>
<tr>
<td>van Wezel-Meijler et al, 2002 (51)</td>
<td>&lt;2 wk of EI to 6 mo CA</td>
<td>BSID version I at 12 mo CA</td>
<td>None reported</td>
<td>Adequate</td>
<td>No</td>
</tr>
<tr>
<td>Fewtrell et al, 2002 (48)</td>
<td>&lt;Day 10 to discharge from hospital (≈32 d)</td>
<td>BSID version II at 18 mo CA</td>
<td>Sepsis, NEC, IVH, BPD, ROP</td>
<td>Adequate</td>
<td>Yes</td>
</tr>
<tr>
<td>Fewtrell et al, 2004 (49)</td>
<td>From 33 wk PMA to 9 mo CA</td>
<td>BSID version II at 18 mo CA</td>
<td>Sepsis, NEC, IVH</td>
<td>Adequate</td>
<td>Yes</td>
</tr>
<tr>
<td>Clandinin et al, 2005 (21)</td>
<td>Day 10 of EI to 12 mo CA</td>
<td>BSID version II at 18 mo CA</td>
<td>NEC, sepsis, IVH, ROP, BPD</td>
<td>Adequate</td>
<td>No</td>
</tr>
<tr>
<td>Fang et al, 2005 (50)</td>
<td>24-wk intervention</td>
<td>BSID version II at 12 mo</td>
<td>None reported</td>
<td>Unclear</td>
<td>No</td>
</tr>
<tr>
<td>Vanderhoof et al, 1999 (52)</td>
<td>≤28 d to 8 wk CA</td>
<td>None reported</td>
<td>NEC, sepsis</td>
<td>Adequate</td>
<td>No</td>
</tr>
<tr>
<td>Carlson, 1992 (46)</td>
<td>≈32 wk PMA to 9 mo CA</td>
<td>BSID version I at 12 mo CA</td>
<td>None reported</td>
<td>Inadequate</td>
<td>No</td>
</tr>
<tr>
<td>Carlson et al, 1998 (53)</td>
<td>&lt;Day 5 to discharge from hospital</td>
<td>None reported</td>
<td>NEC, sepsis, ROP, BPD</td>
<td>Inadequate</td>
<td>No</td>
</tr>
<tr>
<td>Foreman-van Drongelen et al, 1996 (47)</td>
<td>Day 4 to 3 mo CA</td>
<td>None reported</td>
<td>BPD, sepsis, IVH</td>
<td>Unclear</td>
<td>No</td>
</tr>
</tbody>
</table>
infants. Caution is needed when interpreting these data because of the small sample sizes and the large CIs. In addition, both trials that used BSID-I had postrandomization exclusions that could have introduced a systematic error (46, 51). Psychomotor development assessed with the BSID-II had inadequate sample sizes has resulted in questions relating to the dose and source of LCPUFAs. Subgroup analyses based on dose or source were not possible in our meta-analysis.

Although the infant formula industry has invested millions of dollars in trials to support their products, the differences between the trials as well as the fact that many studies have not had adequate sample sizes has resulted in questions relating to the efficacy of LCPUFAs in improving neurodevelopment and to the dose and source of LCPUFAs. Subgroup analyses based on dose or source were not possible in our meta-analyses because of the disparate supplementation regimens across trials (Table 1).

There has been no previous systematic synthesis of the literature to investigate the effect of LCPUFA-supplemented compared with control formula on the incidence of diseases of prematurity. We noted no effect of LCPUFAs on the risk of NEC or sepsis. These data contribute to the growing body of knowledge regarding the safety of LCPUFA-supplemented formulas. Too few data were available to investigate the ROP, IVH, and BPD outcomes, and further studies are necessary to confirm the safety of LCPUFA-enriched formulas in trials with low risk of bias and with sufficient statistical rigor. However, the collection of additional data to compare incidences of disease between the LCPUFA-supplemented and control infants may be unlikely because LCPUFA-supplemented formulas are already widely used in clinical practice.

The aim of these meta-analyses was to specifically focus on core clinical measures of infant health and development. As such, the neurodevelopmental outcomes were assessed with global measures. A limitation of this approach was that we did not include other outcome measures relevant to the developing visual system, growth, behavior, or specific domains of cognition. Furthermore, the systematic review is reflective of the included trials; most trials were restricted to exclusively formula-fed infants (41, 48, 50, 51) or only followed up infants that were predominantly fed the trial formula (12, 21). In practice, however, a large proportion of preterm infants are fed both human milk and formula (58–60), and trials that incorporate the typical feeding patterns of preterm infants are needed because they will have greater external validity. It is not known whether human milk–fed infants who require complementary formula would benefit from LCPUFA-supplemented formulas.

### TABLE 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>N</th>
<th>LCPUFA Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight</th>
<th>WMD (random) 95% CI</th>
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<tr>
<td><strong>01 BSID Version II</strong></td>
<td>106</td>
<td>89.00 (18.40)</td>
<td>54</td>
<td>83.00 (18.20)</td>
<td>2.61 (1.33, 3.89)</td>
<td>12.14</td>
<td>7.70 (5.64, 9.74)</td>
</tr>
<tr>
<td>Clandinin 2005</td>
<td>106</td>
<td>89.00 (18.40)</td>
<td>54</td>
<td>83.00 (18.20)</td>
<td>2.61 (1.33, 3.89)</td>
<td>12.14</td>
<td>7.70 (5.64, 9.74)</td>
</tr>
<tr>
<td>Fewtrell 2002</td>
<td>48</td>
<td>90.00 (18.40)</td>
<td>24</td>
<td>85.00 (18.20)</td>
<td>3.61 (2.10, 5.12)</td>
<td>21.73</td>
<td>9.00 (1.04, 16.96)</td>
</tr>
<tr>
<td>O’Connor 2001</td>
<td>10</td>
<td>90.00 (18.40)</td>
<td>4</td>
<td>85.00 (18.20)</td>
<td>3.61 (2.10, 5.12)</td>
<td>21.73</td>
<td>9.00 (1.04, 16.96)</td>
</tr>
</tbody>
</table>

FIGURE 2. Meta-analysis forest plots showing weighted mean differences (WMDs) in mental (A) and psychomotor (B) development indexes from Bayley Scales of Infant Development (BSID) assessments of preterm infants fed formula supplemented with long-chain polyunsaturated fatty acids (LCPUFAs) or control formula. Subgroup analyses were based on the version of the BSID used for assessments.

MDI, mental development index; PDI, psychomotor development index.
and health outcomes of infants born preterm. Any benefit to neurodevelopmental outcome may be important to this group of vulnerable infants because the mean score of the preterm infants included in these analyses was \( \pm 1 \) SD lower than the standardized norm.

In conclusion, further work is necessary to determine the extent of the benefit of supplemental LCPUFAs on the neurodevelopment and health outcomes of infants born preterm. Any benefit to neurodevelopmental outcome may be important to this group of vulnerable infants because the mean score of the preterm infants included in these analyses was \( \pm 1 \) SD lower than the standardized norm.

**FIGURE 3.** Meta-analysis forest plots comparing the relative risk (RR) of sepsis from all trial data (A) or from trials in which sepsis was confirmed by blood culture (B). LCPUFA, long-chain polyunsaturated fatty acid.

**FIGURE 4.** Meta-analysis forest plots comparing the relative risk (RR) of necrotizing enterocolitis (NEC) from all trial data (A) or from trials in which NEC was confirmed by radiology, surgery, or postmortem examination (B). LCPUFA, long-chain polyunsaturated fatty acid.
TABLE 2
Fixed-effects meta-analyses of retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD) in preterm infants fed preterm formula supplemented with long-chain polyunsaturated fatty acids (LCPUFAs) and in control infants

<table>
<thead>
<tr>
<th>Disease type of analysis</th>
<th>Included trials</th>
<th>Disease frequency (diagnosed/total)</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>I²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP</td>
<td></td>
<td>Control</td>
<td>LCP UF A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any definition</td>
<td>(21, 48, 53)</td>
<td>68/304</td>
<td>103/371</td>
<td>1.23 (0.93, 1.63)</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Internationally accepted definition</td>
<td>(21, 48, 53)</td>
<td>68/304</td>
<td>103/371</td>
<td>1.23 (0.93, 1.63)</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>(48)</td>
<td>3/100</td>
<td>2/95</td>
<td>0.70 (0.12, 4.11)</td>
<td>0.69</td>
<td>NA</td>
</tr>
<tr>
<td>Severe ROP (≥grade 3)</td>
<td>(53)</td>
<td>4/85</td>
<td>1/34</td>
<td>0.63 (0.07, 5.39)</td>
<td>0.67</td>
<td>NA</td>
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<tr>
<td>IVH</td>
<td></td>
<td>Control</td>
<td>LCP UF A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any definition</td>
<td>(21, 47–49)</td>
<td>44/351</td>
<td>64/474</td>
<td>0.87 (0.62, 1.23)</td>
<td>0.43</td>
<td>50.5</td>
</tr>
<tr>
<td>Internationally accepted definition</td>
<td>(21, 48, 49)</td>
<td>44/335</td>
<td>64/459</td>
<td>0.87 (0.62, 1.23)</td>
<td>0.43</td>
<td>50.5</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>(48, 49)</td>
<td>12/216</td>
<td>17/217</td>
<td>1.40 (0.69, 2.84)</td>
<td>0.36</td>
<td>45.5</td>
</tr>
<tr>
<td>Severe IVH (≥grade 3)</td>
<td>(48, 49)</td>
<td>2/216</td>
<td>1/217</td>
<td>0.60 (0.08, 4.55)</td>
<td>0.62</td>
<td>0</td>
</tr>
<tr>
<td>BPD</td>
<td></td>
<td>Control</td>
<td>LCP UF A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any definition</td>
<td>(12, 21, 47, 48, 53)</td>
<td>67/464</td>
<td>104/669</td>
<td>1.10 (0.82, 1.47)</td>
<td>0.52</td>
<td>0</td>
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<tr>
<td>Requirement for oxygen at 36 wk</td>
<td>(21)</td>
<td>17/119</td>
<td>37/242</td>
<td>1.07 (0.63, 1.82)</td>
<td>0.80</td>
<td>NA</td>
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<tr>
<td>Sensitivity analysis</td>
<td>No trials</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

1 NA, not applicable because only one trial; NEC, necrotizing enterocolitis; PMA, postmenstrual age.

The authors’ responsibilities were as follows—LGS, RAG, and MM: designed the systematic review and meta-analysis; LGS; collected data, performed the analyses, and wrote the manuscript under the supervision of MM and RAG; and AM: provided expert advice on neonatal medicine. All authors performed the analyses, and wrote the manuscript under the supervision of MM and RAG and serve on advisory boards of companies that manufacture infant formula. None of the authors had any financial interests in the production or sales of infant formula.

REFERENCES


