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Longchain polyunsaturated fatty acid supplementation in preterm infants (Review)

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[Intervention Review]

Longchain polyunsaturated fatty acid supplementation in preterm infants

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ABSTRACT

Background

Controversy exists over whether longchain polyunsaturated fatty acids (LCPUFA) are essential nutrients for preterm infants because they may not be able to synthesise sufficient amounts of LCPUFA to meet the needs of the developing brain and retina.

Objectives

To assess whether supplementation of formula milk with LCPUFA is safe and of benefit to preterm infants. The main areas of interest were the effects of supplementation on the visual function, development and growth of preterm infants.

Search methods

Trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) in the Cochrane Library (searched 28 February 2016), MEDLINE Ovid (1966 to 28 February 2016), Embase Ovid (1980 to 28 February 2016), CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1980 to 28 February 2016), MEDLINE In Process & Other Non-indexed Citations (1966 to 28 February 2016) and by checking reference lists of articles and conference proceedings. We also searched ClinicalTrials.gov (13 April 2016). No language restrictions were applied.

Selection criteria

All randomised trials evaluating the effect of LCPUFA-supplemented formula in enterally-fed preterm infants (compared with standard formula) on visual development, neurodevelopment and physical growth. Trials reporting only biochemical outcomes were not included.

Data collection and analysis

All authors assessed eligibility and trial quality, two authors extracted data separately. Study authors were contacted for additional information.

Main results

Seventeen trials involving 2260 preterm infants were included in the review. The risk of bias varied across the included trials with 10 studies having low risk of bias in a majority of the domains. The median gestational age (GA) in the included trials was 30 weeks and median birth

weight (BW) was 1300 g. The median concentration of docosahexaenoic acid (DHA) was 0.33% (range: 0.15% to 1%) and arachidonic acid (AA) 0.37% (range: 0.02% to 0.84%).

Visual acuity

Visual acuity over the first year was measured by Teller or Lea acuity cards in eight studies, by visual evoked potential (VEP) in six studies and by electroretinogram (ERG) in two studies. Most studies found no significant differences in visual acuity between supplemented and control infants. The form of data presentation and the varying assessment methods precluded the use of meta-analysis. A GRADE analysis for this outcome indicated that the overall quality of evidence was low.

Neurodevelopment

Three out of seven studies reported some benefit of LCPUFA on neurodevelopment at different postnatal ages. Meta-analysis of four studies evaluating Bayley Scales of Infant Development at 12 months ($N = 364$) showed no significant effect of supplementation (Mental Development Index (MDI): MD 0.96, 95% CI -1.42 to 3.34 ; $P = 0.43$; $I^2 = 71\%$ — Psychomotor Development Index (PDI): MD 0.23, 95% CI -2.77 to 3.22 ; $P = 0.88$; $I^2 = 81\%$). Furthermore, three studies at 18 months ($N = 494$) also revealed no significant effect of LCPUFA on neurodevelopment (MDI: MD 2.40, 95% CI -0.33 to 5.12 ; $P = 0.08$; $I^2 = 0\%$ — PDI: MD 0.74, 95% CI -1.90 to 3.37 ; $P = 0.58$; $I^2 = 54\%$). A GRADE analysis for these outcomes indicated that the overall quality of evidence was low.

Physical growth

Four out of 15 studies reported benefits of LCPUFA on growth of supplemented infants at different postmenstrual ages (PMAs), whereas two trials suggested that LCPUFA-supplemented infants grow less well. One trial reported mild reductions in length and weight z scores at 18 months. Meta-analysis of five studies ($N = 297$) showed increased weight and length at two months post-term in supplemented infants (Weight: MD 0.21, 95% CI 0.08 to 0.33; $P = 0.0010$; $I^2 = 69\%$ — Length: MD 0.47, 95% CI 0.00 to 0.94; $P = 0.05$; $I^2 = 0\%$). Meta-analysis of four studies at a corrected age of 12 months ($N = 271$) showed no significant effect of supplementation on growth outcomes (Weight: MD -0.10 , 95% CI -0.31 to 0.12 ; $P = 0.34$; $I^2 = 65\%$ — Length: MD 0.25; 95% CI -0.33 to 0.84 ; $P = 0.40$; $I^2 = 71\%$ — Head circumference: MD -0.15 , 95% CI -0.53 to 0.23 ; $P = 0.45$; $I^2 = 0\%$). No significant effect of LCPUFA on weight, length or head circumference was observed on meta-analysis of two studies ($n = 396$ infants) at 18 months (Weight: MD -0.14 , 95% CI -0.39 to 0.10 ; $P = 0.26$; $I^2 = 66\%$ — Length: MD -0.28 , 95% CI -0.91 to 0.35 ; $P = 0.38$; $I^2 = 90\%$ — Head circumference: MD -0.18 , 95% CI -0.53 to 0.18 ; $P = 0.32$; $I^2 = 0\%$). A GRADE analysis for this outcome indicated that the overall quality of evidence was low.

Authors' conclusions

Infants enrolled in the trials were relatively mature and healthy preterm infants. Assessment schedule and methodology, dose and source of supplementation and fatty acid composition of the control formula varied between trials. On pooling of results, no clear long-term benefits or harms were demonstrated for preterm infants receiving LCPUFA-supplemented formula.

PLAIN LANGUAGE SUMMARY

Longchain polyunsaturated fatty acid supplementation in preterm infants

Review question: Whether feeding premature babies with formula milk supplemented with longchain polyunsaturated fatty acids (LCPUFA) results in improved vision and overall neurodevelopment.

Background: LCPUFA are a type of fatty acid necessary for the maturation of the brain and retina. Unlike breast milk that contains high levels of LCPUFA, most infant formulae are known to only contain minimal amounts of LCPUFA. Babies fed with breast milk are known to have more mature visual skills and a higher IQ (intelligence quotient) than babies fed with formula milk. It has been suggested that the relatively high levels of LCPUFA found in breast milk may contribute to the higher IQ levels and visual skills. Some milk formulae are available with added LCPUFA, usually as fish oil.

Study characteristics: Studies that compared the outcomes of premature babies (born at < 37 weeks of pregnancy) who were given formula milk enriched with LCPUFA versus formula milk without enrichment with LCPUFA were analysed in this review.

Key results: The researchers found that premature babies fed formula milk supplemented with LCPUFA do not have better outcomes compared to those fed formula milk without LCPUFA.

Quality of evidence: The overall quality of evidence was considered low.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

LCPUFA supplemented formula compared with standard formula for clinical outcomes (visual function, neurodevelopment and physical growth)

Patient or population: Preterm infants on enteral feed

Settings: Neonatal Intensive Care Units

Intervention: LCPUFA supplemented formula

Comparison: Standard Formula

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard milk formula	LCPUFA supplemented milk formula				
Visual acuity at 12 months post-term (log/cycles/degree)	Data could not be pooled	Data could not be pooled	NA	82	⊕⊕⊕⊕ Low	Downgraded 2 levels due to very small sample, unclear random sequence generation in one of the RCTs. Meta-analysis could not be performed.
Bayley MDI at 12 months post-term	The mean MDI ranged across control groups from 90.5 to 111.5	The mean MDI ranged across the intervention groups from 92 to 110.1	MD: 0.96 (95% CI: -1.42 to 3.34)	364 (4 RCTs)	⊕⊕⊕⊕ Low	Downgraded 2 levels. Reasons: small sample, unclear allocation concealment and random sequence generation in 2 of the RCTs, and very small effect size (MD) and high statistical heterogeneity ($I^2 = 71\%$)
Bayley PDI at 12 months post-term	The mean PDI ranged across control groups from 86.3 to 102.1	The mean PDI ranged across the intervention groups from 82.2 to 98	MD: 0.23 (95% CI: -2.77 to 3.22)	353 (4 RCTs)	⊕⊕⊕⊕ Low	Downgraded 2 levels. Reasons: small sample, unclear risk of allocation concealment in 2 of the RCTs. Very small effect size (MD) and high statistical heterogeneity ($I^2 = 81\%$).
Weight at 12 months post-term (kg)	The mean weight ranged across control groups from 8.85 kg to 9.62 kg	The mean weight ranged across the intervention groups from 9.02 kg to 9.36 kg	MD: -0.10 (95% CI: -0.31 to 0.12)	271 (4 RCTs)	⊕⊕⊕⊕ Low	Downgraded 2 levels. Reasons: small sample, high or unclear risk of attrition bias in 3 studies and unclear method of randomisation in 1 study. Very small effect size (MD) and high statistical heterogeneity ($I^2 = 65\%$)

Length at 12 months post-term (cm)	The mean length ranged across control groups from 73.2 cm to 74.6 cm	The mean length ranged across the intervention groups from 73.1 cm to 75.5 cm	MD: 0.25 (CI: -0.33 to 0.84)	271 (4 RCTs)	⊕⊕⊕⊕ Low	Downgraded 2 levels. Reasons: small sample, high or unclear risk of attrition bias in 3 included studies and unclear method of randomisation in 1 study. Very small effect size (MD) and high statistical heterogeneity ($I^2 = 71\%$)
Head circumference at 12 months post-term (cm)	The mean head circumference ranged across control group from 45.8 cm to 46.43 cm	The mean head circumference ranged across the intervention groups from 45.9 cm to 46.31 cm	MD: -0.15 (CI: -0.53 to 0.23)	271 (4 RCTs)	⊕⊕⊕⊕ Low	Downgraded 2 levels. Reasons: small sample, high or unclear risk of attrition bias in 3 included studies and unclear method of randomisation in one study. Very small effect size (MD).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Dietary fat in infancy is fundamental for the provision of energy, fat soluble vitamins and essential fatty acids (EFA). However, the type of fat required is controversial and interest has recently focused on the importance of longchain polyunsaturated fatty acids (LCPUFA) such as docosahexaenoic acid (DHA) and arachidonic acid (AA). These fatty acids are found in high proportions in the structural lipids of cell membranes, particularly those of the central nervous system, and their accretion primarily occurs during the last trimester of pregnancy and the first year of life (Clandinin 1980).

During pregnancy, DHA and AA cross the placenta to the fetus. Postnatally these fatty acids are supplied in breast milk, which contains a full complement of all PUFA including precursors and metabolites. However, most infant formulae contain only the precursor EFA (alpha linoleic acid (ALA; omega 3 precursor) and linoleic acid (LA; omega 6 precursor)) from which formula-fed infants must synthesise their own DHA and AA respectively. The absence of LCPUFA in formula may be further exacerbated by inhibition of incorporation of endogenously produced LCPUFA by the high concentrations of LA currently in most formulae.

Description of the intervention

Biochemical studies in both term and preterm infants indicate that formula-fed infants have significantly less DHA and AA in their erythrocytes relative to those fed breast milk (Clark 1992). This suggests that infant formula containing only LA and ALA may not be effective in meeting the full EFA requirements of infants.

Biochemical studies of LCPUFA are clinically relevant as dietary fatty acid supply may affect physiological function. In observational studies, term infants fed breast milk have been found to have more mature visual acuities and higher DHA levels than those receiving formula. Further, their visual acuities were positively correlated with erythrocyte DHA levels (Makrides 1993).

How the intervention might work

Evidence to suggest that breast-fed infants have a long-term IQ advantage over those who have been fed formula has been evident in the literature for many years (Morrow-Tlucak 1988; Lucas 1992; Anderson 1999; Kramer 2008). As most of these studies are not randomised, the majority of comparisons between breast-fed and formula-fed infants are confounded by genetic and socioeconomic factors. These studies do not relate their findings to fatty acid supply. However, some reports suggest that the low levels of LCPUFA, such as DHA, found in formula-fed infants may contribute to the lower IQ scores reported in formula-fed infants (Neuringer 1986; Bjerve 1992).

Why it is important to do this review

There are few prospective studies investigating the effect of DHA supply on long-term development. Randomised trials comparing standard formula and supplemented formula are necessary to

address the issue of whether LCPUFA are essential nutrients in infancy before supplementation of formula with LCPUFA becomes routine, at considerable cost without the long-term risks and benefits being determined.

OBJECTIVES

To assess whether supplementation of formula milk with LCPUFA is safe and of benefit to preterm infants. The main areas of interest were the effects of supplementation on the visual function, development and growth of preterm infants.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised clinical trials (RCTs) with at least six weeks of follow-up were considered.

Types of participants

Trials involving enterally-fed preterm (<37 weeks gestation) infants were considered.

Types of interventions

Different LCPUFA supplements were included as different oils have been used to increase the DHA levels in the plasma and erythrocytes of infants (e.g. fish, fungal and egg phospholipid).

Types of outcome measures

Trials with clinical outcomes (visual development, neurodevelopment and physical growth) were included. Trials reporting only biochemical outcomes were not included.

Search methods for identification of studies

For the previous versions of this Cochrane review, trials were identified by searching MEDLINE (1966 to December 2009), the Cochrane Central Register of Controlled Trials (CENTRAL; 2009, Issue 4) in the Cochrane Library, and by checking reference lists of articles and conference proceedings.

For the 2016 update of this review, five databases were searched.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) in the Cochrane Library (searched 28 February 2016); (Appendix 1);
- MEDLINE Ovid (2008 to 28 February 2016); (Appendix 2);
- Embase Ovid (2008 to 28 February 2016); (Appendix 3);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 2008 to 28 February 2016); (Appendix 4);
- MEDLINE (In-Process & Other Non-indexed Citations) (2008 to 28 February 2016); (Appendix 5).

We also searched ClinicalTrials.gov (13 April 2016) using search terms fatty acid and infant. There was no language restriction imposed. See [Figure 1](#)

Figure 1. Study flow diagram.

Data collection and analysis

At least two of the review authors independently compiled and completed data collection forms. We contacted authors of 10 studies in writing to clarify existing data or to provide missing data and we received responses from five ([Lapillonne 2000](#); [O'Connor 2001](#); [Koletzko 2003](#); [Clandinin 2005](#); [Groh-Wargo 2005](#)).

Selection of studies

All randomised trials of formula milk supplemented with LCPUFA and with clinical endpoints were reviewed.

Data extraction and management

Two of the review authors separately extracted, assessed and coded all data for each study using a form that was designed specifically for this review. For each included study the authors collected information regarding the method of generating random sequence numbers, allocation concealment, blinding, intervention, stratification, whether the trial was conducted at a single centre or multiple centres, information regarding inclusion criteria (including gestational age) and postnatal age at the time of treatment. The authors resolved differences in assessment by discussion. For each study, one review author entered final data

into Review Manager 5 (RevMan) and then a second review author checked the data. Any disagreements were addressed by consensus after discussion with all authors.

Assessment of risk of bias in included studies

Two review authors (KM and SR) independently assessed the risk of bias (low, high, or unclear) of all included trials using the [Higgins 2011](#) Cochrane 'Risk of bias' tool for the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

Any disagreements were resolved by discussion or by a third assessor. See [Appendix 6](#) for a more detailed description of risk of bias for each domain.

Measures of treatment effect

The standard methods of the Cochrane Neonatal Review Group were used. Statistical analyses were performed using RevMan software. Categorical data were analyzed using relative risk (RR), risk difference (RD) and the number needed to treat for an additional beneficial outcome (NNTB). Continuous data were analyzed using mean difference (MD). The 95% confidence interval (CI) was reported on all estimates.

Unit of analysis issues

If available, we planned to combine results from cluster trials with other trials using generic inverse variance methods.

Dealing with missing data

If participant dropout led to missing data then we planned to conduct intention-to-treat analyses. We endeavoured to obtain missing data from the trial authors.

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments).

Assessment of reporting biases

If at least 10 studies were included in the meta-analysis we planned to assess publication bias using the funnel plot ([Egger 1997](#)).

Data synthesis

The meta-analysis was performed using RevMan software, supplied by Cochrane. For estimates of typical relative risk and risk difference, we used the Mantel-Haenszel method. All meta-analyses were done using the fixed-effect model.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook ([Schünemann 2013](#)), to assess the quality of evidence for the following (clinically relevant) outcomes at one year of age: visual acuity (based on VEP); physical growth (weight, length and head circumference); and neurodevelopmental outcomes (Bayley Scales of Infant Development-2).

Two authors (KM and SR) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised controlled trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the [GRADEpro](#) Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: 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.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were performed.

RESULTS

Description of studies

Seventeen trials were included in this review and are summarised in the '[Characteristics of included studies](#)' table. Details of the 16 excluded studies are summarised in the '[Characteristics of excluded studies](#)' table ([Donzelli 1996](#); [Lim 2002](#); [Koletzko 2003](#); [Rodriguez 2003](#); [Smithers 2008a](#); [Smithers 2008b](#); [Makrides 2009](#); [Shah 2009](#); [Collins 2010](#); [Smithers 2010](#); [Collins 2011](#); [van de Lagemaat 2011](#); [Almaas 2015](#); [Alshweki 2015](#); [Collins 2015](#); [Baack 2016](#)).

The composition and dose of LCPUFA supplement varied. Some studies supplemented with only omega-3 (n-3) fatty acids ([Carlson 1992](#); [Carlson 1996](#)), while the majority used n-3 and omega-6 (n-6) fatty acids ([Uauy 1990](#); [Fadella 1996](#); [Clandinin 1997](#); [Diersen-Schade 1998](#); [Vanderhoof 1999](#); [Lapillonne 2000](#); [O'Connor 2001](#); [Fewtrell 2002](#); [Innis 2002](#); [van Wezel 2002](#); [Fewtrell 2004](#); [Clandinin 2005](#); [Fang 2005](#); [Groh-Wargo 2005](#); [Carnielli 2007](#)). If infants were randomised to more than one supplement, the supplement that contained both n-3 and n-6 LCPUFA was selected for the comparison over one containing only n-3 ([Innis 2002](#)). If the two supplements were n-3 and n-6 as fish/fungal oil or egg-TG/fish oil, we chose the fish/fungal group as microbial oils are more similar to human milk fat than egg-TG ([O'Connor 2001](#); [Clandinin 2005](#);

Groh-Wargo 2005). For this review, if more than one control group was included, the control group receiving a formula with a LA:ALA ratio most like breast milk was selected (Uauy 1990; Fadella 1996; Clandinin 1997; Vanderhoof 1999; Lapillonne 2000).

Risk of bias in included studies

The risks of bias in the included trials were assessed predominantly based on random sequence generation, allocation concealment, blinding of intervention, blinding of outcome assessment, and completeness of follow-up, giving attention to the possibility of selection bias, performance bias, exclusion bias and detection bias. Details of the risk of bias of the included studies are described in the 'Characteristics of included studies' table.

We assessed Uauy 1990, Carlson 1992, Clandinin 1997, Lapillonne 2000, O'Connor 2001, Fewtrell 2002, Innis 2002, van Wezel 2002, Vanderhoof 1999, Fewtrell 2004 and Groh-Wargo 2005 as having low risk of bias in the majority of the domains. Clandinin 2005 had low follow-up rates (44% to 60%). Fang 2005 and Carnielli 2007 had small sample size ($N = 28$ and $N = 22$, respectively) and uncertainty regarding adequacy of allocation concealment and method of randomisation. The developmental assessment tool changed in the middle of the Carlson 1996 trial whereas Fadella 1996 used methodologies for visual evoked potential (VEP) and electroretinogram (ERG) assessments that deviate from generally accepted international standards. We could not assess risk of bias of Diersen-Schade 1998 as only the abstract was available. See Figure 2 for summary of risk of bias in included trials.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Effects of interventions

See: [Summary of findings for the main comparison](#)

Visual development – assessment methods

Visual acuity is a measure of the smallest element that can be resolved and may be assessed in infants by using gratings which consist of black and white stripes or checkerboard patterns. Grating acuity can be measured by using behavioural (Teller acuity cards) or visual evoked potential (VEP) methods. Each pairing of a black and white stripe is referred to as a cycle and the spatial frequency of a grating is defined by the number of cycles per degree of viewing angle. As grating spatial frequency increases, the stripes become finer and are more difficult to discriminate, eventually appearing as an even grey to the observer. Grating acuity is the highest spatial frequency where the stripes can be resolved.

The VEP is the electrical activity of the brain that is generated in response to a reversing contrast checkerboard or grating. The VEP is recorded from an electrode placed over the occipital pole. The amplitude of the VEP increases linearly with spatial frequency near the visual acuity threshold. Linear regression is used to fit a straight line through the linear portion of the VEP amplitude versus spatial frequency curve and visual acuity is determined from the intercept

of the regression line with the spatial frequency axis. Studies in this review have used different methods for assessing VEP (transient, steady state and sweep VEP). Transient VEP reflects a slow pattern reversal rate and records individual responses where the brain has time to recover after each reversal. A steady state VEP reflects a quick pattern reversal rate in which the next evoked response is actually evoked before the previous one has finished. The evoked responses hence run into each other so the output looks almost like a sine wave. The faster the reversal rate the more condensed the wave. The sweep/swept VEP is also a steady state technique but uses a different stimulus — usually stripes (instead of checks) that sweep through from the largest to the smallest in about 10 seconds.

Behavioural methods for assessing visual acuity rely on the strong preference shown by infants for patterned stimuli over non-patterned stimuli. Both the acuity card procedure (ACP) and the forced preferential looking (FPL) procedure have been used in conjunction with Teller acuity cards for measuring the development of visual acuity in infants. The FPL procedure tests binocular grating acuity: the tester views the infant behind a blind through a peephole, without knowledge of the spatial-frequency gratings on the cards, and makes a forced-choice judgement about which card the infant prefers. Individual acuities are converted to log cycles/degree and SD are in octaves which are determined by

dividing one log SD by 0.3. The Lea acuity cards test uses a similar methodology but does not require blinds between examiner and child. The 'Hiding Heidi' low contrast test is a contrast sensitivity test using pictures with facial features (i.e. 'Hiding Heidi') presented at varying levels of contrast. The child's physical response to a particular card suggests the child sees 'Hiding Heidi' at that level of contrast.

Electroretinography, and its resultant ERG, is a method of assessment of retinal function. The more mature the retinal function, the lower the threshold required to elicit a response, and the higher the maximum amplitude recorded (threshold and Vmax are reported in log units).

For this review, most of the visual data is analyzed as mean $\pm$ SD in log values. This form of data presentation and the varying assessment methods preclude the use of meta-analysis.

Visual development – results

Visual acuity using Teller cards was measured in the [Carlson 1992](#) and [Carlson 1996](#) studies. In the 1992 study, the supplement was fed until 12 months and visual acuity was better in the supplemented group at two and four months post-term but not at six, nine, and twelve months (the data are published in Figures only and therefore cannot be included in the Tables for this review). In the 1996 study, LCPUFA supplementation was fed until two months post-term and visual acuity assessed over 12 months post-term. At two months, the supplemented infants without bronchopulmonary dysplasia (BPD) had better visual acuity compared with control but supplemented infants with BPD had poorer visual acuity compared with control. No differences between supplemented and control groups (with or without BPD) were detected at four, six, nine and twelve months.

In the [Diersen-Schade 1998](#) study, visual acuity was also assessed with Teller acuity cards and no difference was documented between supplemented and control infants at two and four months post-term. [Fadella 1996](#) assessed vision using the flash VEP; waveforms of the supplemented group were of different morphology and some of shorter latency than those of the control group – the latencies of N4 and P4 were shorter in the supplemented group but the latencies of N2, P2, N3 and P3 were not significantly different between the groups. There are concerns with the methodology of assessment in this study in that it deviates from international standards (International Society for Clinical Electrophysiology of Vision). Therefore, the data reported are difficult to interpret and sensitivity may have been decreased

so much that changes due to the intervention may not have been detected.

[Uauy 1990](#) measured visual acuity at two months post-term using VEP and Teller acuity cards and report that the LCPUFA-supplemented infants had better visual acuity (data were not available for this review). [Uauy 1990](#) also assessed retinal function. The authors used contact lens electrodes and dark-adapted all subjects to measure rod ERG. They demonstrated that Vmax for rod function measured by the ERG was higher in supplemented infants when compared with control infants at 36 weeks' postmenstrual age (PMA) but there were no significant differences at four months post-term. The function of the cones, which are more mature at birth, was not affected (data not included in this review).

[Fadella 1996](#) measured ERG at 52 weeks' PMA or three months post-term. There were no significant differences between the groups in ERG (a and b latencies, and a-b amplitude); however, subjects were not dark-adapted, their pupils were not dilated and electrodes were placed on the forehead instead of using contact lens or gold foil electrodes. [Fadella 1996](#) also measured auditory-evoked responses at 52 weeks' PMA and found no differences between the groups (nine latencies measured; these results are not listed in this review but are available in the publication).

[Innis 2002](#) measured visual acuity (Teller acuity cards) at two and four months post-term and found no difference between supplemented and control groups.

[O'Connor 2001](#) measured visual acuity by Teller acuity cards at two, four and six months post-term and found no difference between supplemented and control groups. However, swept-parameter VEP was better in the supplemented groups compared with control group in a subgroup of infants at six months post-term. [van Wezel 2002](#) also reported no significant differences in visual acuity between the supplemented and control groups at three and twelve months post-term by flash VEP and at three, six, twelve and fourteen months post-term by Teller acuity cards. However, the sample size in this study was small and calculated on cerebral myelination assessed by magnetic resonance imaging. They found no significant difference in cerebral myelination between groups.

[Fang 2005](#) measured visual acuity by steady state VEP, response to Lea grating acuity cards and 'Hiding Heidi' low contrast cards at four and six months after enrolment and found no difference between supplemented and control groups.

The form of data presentation and the varying assessment methods precluded the use of meta-analysis ([Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Supplement vs control, outcome: 1.6 Visual acuity (log cycles/degree) at 12 months post-term.

Neurodevelopment

Carlson 1992 and Carlson 1996 reported the results of the Fagan Infantest of development at 12 months. Data were also published at six and nine months for the 1993 study but were not included in this review. The Fagan Infantest measures novelty preference based on the observation that after habituation to a familiar stimulus has occurred, a preference will be shown for a different (novel) stimulus if both the familiar and novel stimuli are presented together. A novelty preference score is derived for the average percent of total time spent viewing the novel stimuli on ten discrete paired comparison tests. Infants with average scores of greater than 57% are said to have a significant novelty preference, that is the time spent looking at the novel stimuli compared with that spent looking at the familiar stimuli is greater than by chance alone. Novelty preference has been interpreted as an early measure of information-processing capacity (Fagan 1970). Only a subset of the Carlson 1996 cohort was assessed by the same version of the Fagan test as the Carlson 1992 cohort and so the meta-analysis was limited to the subset of the 1996 cohort. Contrary to their hypothesis, novelty preference was lower in the supplemented group. However, the number of looks was higher and the duration of each look was shorter in the supplemented group, which the investigators thought may indicate better cognition.

The Carlson 1992 study reported Bayley developmental scores at 12 months. Mean Psychomotor Development Index (PDI) was lower in the supplemented group. Fewtrell 2002 reported Bayley Scales of Infant Development (BSID) and Knoblock, Passamanik & Sherrard's Developmental Screening Inventory at nine and 12 months and found no difference between groups. O'Connor 2001 measured BSID at 12 months and van Wezel 2002 at 12 and 24 months post-term and no significant differences were reported between groups (Figure 4; Figure 5). Clandinin 2005 reported BSID at 18 months post-term and found a trend towards higher Bayley MDI and PDI in algal/fungal oil-supplemented versus control infants. Fang 2005 measured BSID at 6 and 12 months post-term and found higher MDI scores (mean difference 8.2 points, 95% CI 2.31 to 14.09) and PDI scores (mean difference 11.3 points, 95% CI 3.51 to 19.09) in the supplemented versus control group at 12 but not six months. Fewtrell 2004 reported Knoblock, Passamanik & Sherrard's Developmental Screening Inventory at 9 months, and BSID at 18 months post-term and found no significant difference between groups. In the pre-specified subgroup analysis of boys, Bayley MDI but not PDI at 18 months was higher in the supplemented versus control group (mean difference 5.7 points, 95% CI 0.30 to 11.10).

Figure 4. Forest plot of comparison: 1 Supplement vs control, outcome: 1.13 Bayley MDI at 12 months post-term.

Figure 5. Forest plot of comparison: 1 Supplement vs control, outcome: 1.14 Bayley PDI at 12 months post-term.

Isaac 2011 reported 10-year follow-up of [Fewtrell 2004](#): when general and specific cognition including intelligence, neuropsychological assessment, memory, academic attainments, attention and executive function were assessed on 57/116 control and 50/122 LCPUFA-supplemented subjects, no significant differences were found. In planned subgroup analyses, significantly higher scores in verbal IQ, full-scale IQ and word-pair learning were reported in the LCPUFA-supplemented group who received no maternal breast milk. Furthermore, in planned gender analyses, girls showed beneficial effects of LCPUFA on 2/20 domains that were assessed (i.e. word reading score and spelling score).

Meta-analysis of BSID of four studies at 12 months ($N = 364$, [Figure 4](#) and [Figure 5](#)) and three studies at 18 months ($N = 494$) post-term showed no significant effect of supplementation on neurodevelopment ([Analysis 1.37](#); [Analysis 1.38](#)).

Physical growth

Growth was measured in fifteen studies. In [Carlson 1992](#), data were taken from the published figures of z-scores, as only mean absolute values were published. Z-scores are normalised growth parameters and express growth in standard deviations from the mean.

Data from the [Carlson 1992](#) and [Carlson 1996](#) studies suggest that normalised weight (but not length and head circumference) is lower in preterm infants who receive supplemented formula when compared with controls. In the [Uauy 1990](#), [Fadella 1996](#), [Clandinin 1997](#) and [Vanderhoof 1999](#) studies, growth (weight, length and head circumference) was not affected by the supplement. In the [Diersen-Schade 1998](#) trial, weight was higher at two months post-term in the supplemented group compared with controls, but not significantly different at four months post-term. [O'Connor 2001](#) measured anthropometrics at term, two, four, six, nine and 12 months post-term and reported change in weight, length and head circumference over time. They reported no significant difference in growth parameters between supplemented and control groups (when comparing 'intent to treat' groups and subgroups who received more than 80% enteral feed as trial formula). Of interest: length gain was greater among infants weighing less than 1250 g in the control group when compared to the supplemented group (5.74 vs 5.67 mm/wk, $P = 0.008$).

[Innis 2002](#) measured growth at term, two and four months and found supplementation enhances weight and length gains (data for head circumference not given). [Vanderhoof 1999](#) measured growth at term, two and 12 months and found no difference between the groups. [Lapillonne 2000](#) measured weight, length and head circumference at study entry, discharge, term, three and six months post-term and found no difference between the groups. [Fewtrell](#)

[2002](#) found no difference in z-scores but a reduction in absolute weight and length in the supplemented group at 18 months post-term. [Clandinin 2005](#) measured weight, length and head circumference from term to 18 months post-term. Supplemented infants had increased weight at 12 months and greater length at 2, 9 and 12 months. There were no differences in head circumference at any given time point between supplemented and control infants. [Fang 2005](#) measured anthropometrics at one, two, three, four, five, six and 12 months after enrolment and found no difference between groups. [Fewtrell 2004](#) measured weight, length and head circumference at discharge from the hospital, and at nine months and 18 months post-term and found no difference between groups at any given time point, although weight gain and length gain between birth and nine months post-term were greater in the supplemented group when compared to the control group (weight gain: mean difference 310 g, 95% CI 30 to 590; length gain: mean difference 0.9 cm, 95% CI 0.02 to 1.90). In the pre-specified subgroup analysis of boys, weight and weight gain to 9 months and length gain to 18 months were higher in the supplemented group when compared to the control group. [Groh-Wargo 2005](#) measured anthropometrics at term, four and 12 months post-term and found no difference between groups. [Carnielli 2007](#) measured weight at seven months' postnatal age and found no difference between groups.

Kennedy 2010 reported the 10-year follow-up of 45% of infants from the [Fewtrell 2004](#) study: no difference in growth and body composition between the LCPUFA and control were observed. However in a planned gender-specific analysis, LCPUFA-supplemented girls had significantly higher blood pressure, weight, weight SD score, height, head circumference (and SD score), suprailiac and biceps skin fold thicknesses. The result remained consistent when confounders (social code, mother's age) were adjusted. Differences in blood pressures were not significant following adjustment for current weight.

Combining results indicated that infants had increased length at two months post-term ([Uauy 1990](#); [Carlson 1996](#); [Vanderhoof 1999](#); [Innis 2002](#); $n = 297$; [Analysis 1.22](#)) and increased weight at two months post-term ([Uauy 1990](#); [Carlson 1996](#); [Diersen-Schade 1998](#); [Vanderhoof 1999](#); [Innis 2002](#); $n = 485$; [Analysis 1.21](#)) but no effect on head circumference ([Uauy 1990](#); [Carlson 1996](#); [Vanderhoof 1999](#); $n = 187$; [Analysis 1.23](#)). Reduction of weight z-scores in supplemented infants was only reported in [Carlson 1992](#) and [Carlson 1996](#) at 12 months ($n = 116$). Meta-analysis of four studies at 12 months ($N = 271$, [Figure 6](#), [Figure 7](#) and [Figure 8](#)) and two studies at 18 months ($N = 396$; [Analysis 1.46](#); [Analysis 1.47](#); [Analysis 1.48](#)) post-term showed no significant effect of supplementation on weight, length or head circumference.

Figure 6. Forest plot of comparison: 1 Supplement vs control, outcome: 1.28 Weight at 12 months post-term (kg).

Figure 7. Forest plot of comparison: 1 Supplement vs control, outcome: 1.29 Length at 12 months post-term (cm).

Figure 8. Forest plot of comparison: 1 Supplement vs control, outcome: 1.30 Head circumference at 12 months post-term (cm).

Side effects

Uauy 1990 found no significant difference in bleeding time between groups at 34 weeks' postconceptional age (2.15 ± 0.69 , $n = 22$ vs 1.68 ± 0.66 , $n = 20$). There were no differences in bleeding time at four months post-term (Analysis 1.36). They also measured lipid peroxidation status by malonyl dialdehyde production (thiobarbituric acid reactive substances (TBARS)) and by fragility determination of peroxide-stressed red blood cell (RBC) and found no difference between LCPUFA supplemented and control groups (5.33 ± 1.00 , $n = 30$ vs 7.24 ± 0.97 , $n = 28$ (TBARS -azide/+azide $\times 100\%$); Analysis 1.34; Analysis 1.35). Similarly, there was no difference between the groups in membrane fluidity assessed by diphenylhexatriene fluorescence polarisation.

DISCUSSION

Summary of main results

Data from 17 RCTs (2260 preterm infants) does not indicate a long-term benefit of LCPUFA supplementation of formula on visual development, neurodevelopment or physical growth of preterm infants.

Visual acuity was measured by Teller and Lea acuity cards in eight studies, by visual evoked potential (VEP) in six studies and by electroretinography in two studies. Most studies found no differences in visual outcomes between supplemented and control infants (exceptions were Uauy 1990 and O'Connor 2001, where VEP acuity was more mature at two months post-term, and at 6 months post-term in a subgroup of supplemented infants respectively).

The Fagan Infantest measures novelty preference which, under controlled conditions, has moderate predictive validity for performance in standardised intelligence tests in childhood (Fagan

1983). Normal infants should have a novelty preference with the mean novelty preference for term infants being 62%. [Carlson 1992](#) and [Carlson 1996](#) demonstrated lower novelty preferences in the supplemented compared with the control group. Despite this, the investigators concluded that supplemented preterm infants may have more rapid visual information processing given that they took more looks and each look was of shorter duration. Most other studies assessed neurodevelopment by BSID with three out of seven studies reporting some benefit of LCPUFA in different populations of supplemented infants at different postnatal ages ([Fewtrell 2004](#); [Clandinin 2005](#); [Fang 2005](#)).

Four out of fifteen studies reported benefits of LCPUFA on growth of supplemented infants at different postnatal ages ([Diersen-Schade 1998](#); [Innis 2002](#); [Fewtrell 2004](#); [Clandinin 2005](#)). However, [Carlson 1992](#) and [Carlson 1996](#) suggest that preterm infants fed n-3 LCPUFA supplements grow less well than controls and they give some evidence that poor growth in their studies may be due to a reduction in AA levels which occurs when n-3 supplements alone are used. Recent studies add AA to the supplement and usually find no significant negative effect on growth. The only exception is [Fewtrell 2002](#) where mild reductions in length and weight z-scores were reported at 18 months. Contrary to these results, meta-analysis of five studies ([Uauy 1990](#); [Carlson 1996](#); [Diersen-Schade 1998](#); [Vanderhoof 1999](#); [Innis 2002](#)) showed increased weight and length at two months post-term in supplemented infants ([Analysis 1.21](#); [Analysis 1.22](#)).

Recently, there has been discussion as to whether LCPUFA supplementation has gender-specific effects. The latest findings from [Fewtrell 2004](#) study participants at 10 years ([Kennedy 2010](#) and [Isaacs 2011](#)) reported that girls who received LCPUFA-supplemented formula had greater weight, length, head circumference and blood pressure at 10 years. The girls who received LCPUFA-supplemented formula also had better scores on word reading scores and spelling scores. However, the results need to be interpreted with caution since the sample size was extremely small (maximum total N = 68 girls). It is also important to note that in contrast to the 10-year outcomes of [Fewtrell 2004](#) where girls had better cognitive scores, in the original [Fewtrell 2004](#) study, boys who received LCPUFA supplementation experienced beneficial effects on cognition with higher Bayley MDI scores (LCPUFA 86.4 (13.9) vs controls 80.8 (13.0); $p = 0.04$). The DINO trial ([Makrides 2009](#)) that compared high-dose versus low-dose DHA in preterm infants showed higher MDI scores at 18 months of age in girls supplemented with high-dose DHA compared to girls who received low-dose DHA. However, at seven years of age, girls who received high-dose DHA had poorer executive function and behaviour compared to girls who received low-dose DHA ([Collins 2015](#)). Hence, when the results of [Fewtrell 2004](#) and [Makrides 2009](#) are considered together, it appears that there are no consistent gender-specific differences in the outcomes for LCPUFA supplementation.

Overall, this meta-analysis found no clear long-term benefits on visual or intellectual development. The justification for adding LCPUFA to formula is based on the rationale of mimicking the composition of human milk and not on evidence of important clinical benefits. A supplement containing a balance of n-3 and n-6 LCPUFA is unlikely to impair the growth of preterm infants.

Overall, methodology varied considerably between studies making a summary of the combined data difficult. Some of the disparity

between findings may be due to different combinations of LCPUFA in the supplement and different concentrations of EFA in the control formula. Higher ALA and lower LA:ALA will favour DHA synthesis. Another variable is the medical complications and treatments associated with preterm birth with most studies only enrolling relatively healthy formula-fed infants.

In the recent years, a number of systematic reviews and meta-analyses have been conducted to evaluate the effect of LCPUFA in preterm neonates, the details of which are given below. The results have been inconsistent.

[Qawasmi 2012](#) conducted a meta-analysis of 19 RCTs (12 term and 7 preterm RCTs) and concluded that LCPUFA supplementation improves visual acuity up to 12 months of age. However, the benefits were not statistically significant for the subgroup of preterm infant RCTs.

[Beyerlein 2010](#) conducted an individual patient data (IPD) meta-analysis of 870 infants from four large RCTs (two preterm RCTs and two term RCTs) of LCPUFA supplementation in formula. For preterm infants, they reported no significant differences in BSID scores at 18 months of age between the LCPUFA and control groups (N = 341, mean difference for MDI scores 1.9, 95% CI -1.3 to 5.0; mean difference for PDI scores -0.2, 95% CI -3.2 to 2.7).

[Jiao 2014](#) evaluated the role of DHA on cognitive function in infants, children and adults by conducting an extensive systematic review. They found that DHA supplements improved PDI and MDI scores in infants, but the included studies were term infants, not preterm.

Possible reasons for the inconsistent results from RCTs were discussed by [Meldrum 2011](#). They hypothesized that variable sample size, genetic and gender differences, dose and duration of supplementation, compliance and test selections may be the reasons behind the inconclusive findings in these RCTs.

Currently, the research focus seems to have shifted paradigm to identify the optimal dose of DHA rather than comparing LCPUFA formulae to non-supplemented formulae. This is based on the finding that the DHA requirement in the neonatal period substantially exceeds that delivered by typical feeding (breastmilk or formula milk) in preterm infants ([Makrides 2015](#)). However, the RCTs of high-dose DHA supplements given to breast milk-fed preterm infants have also reported inconsistent effects of supplementation on neurodevelopmental and visual outcomes ([Henriksen 2008](#); [Smithers 2008a](#); [Makrides 2009](#); [Smithers 2010](#); [Almaas 2015](#); [Alshweki 2015](#); [Collins 2015](#)).

Overall completeness and applicability of evidence

There is inadequate evidence to support the supplementation of formula milk with LCPUFA for preterm infants.

Quality of the evidence

Overall, the quality of evidence was considered low, given the small sample size of the included studies, high or unclear risk of bias in some of the included studies and high statistical heterogeneity.

Potential biases in the review process

None to our knowledge.

Agreements and disagreements with other studies or reviews

The results of this Cochrane review are consistent with the [Beyerlein 2010](#) and [Qawasmi 2012](#) reviews, which found no significant benefit of LCPUFA supplementation in preterm infants.

AUTHORS' CONCLUSIONS

Implications for practice

The data from RCTs does not support the suggestion that supplementation of formula milk with LCPUFA is beneficial for the visual and neurological development of preterm infants.

Implications for research

There is no consistent evidence supporting the use of LCPUFA supplementation in preterm formula and yet most formulae are currently supplemented with LCPUFA. In future trials, large sample sizes are recommended with subgroup analyses such as maternal factors, gender and genetics. The optimal dose for

LCPUFA supplementation should be determined and the outcomes should be assessed using well-designed and valid measures.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Carlson 1992

Methods	Randomised controlled study, single centre, Memphis. Intervention and outcome assessment were blinded and follow-up of subjects was complete.
Participants	Entry criteria included no need for mechanical ventilation and no significant IVH or retinopathy of prematurity. 10 subjects who could not tolerate enteral feeds were replaced. 79 infants were enrolled, 67 completed study (33 supplemented, 34 control). Subjects were predominantly from lower socio-economic groups and black. Supplemented group GA 29 ± 2 wk, BW 1074 ± 193 g. Control group GA 29 ± 2 wk, BW 1133 ± 163 g.
Interventions	Preterm formula (PT) until discharge (approximately 1800 g) then term formula (T). Supplemented formula 18.7% & 32.6% (PT & T) LA, 3.1% & 4.9% (PT & T) ALA, 0.3% EPA, 0.2% DHA. Control formula 19.1% & 33.1% (PT & T) LA, 3.0% & 4.8% (PT & T) ALA.
Outcomes	Visual acuity (Teller acuity cards) and growth at term (0 months), and 2, 4, 6.5, 9 & 12 months post-term. Fagan infant test at 6.5, 9 and 12 months post-term. Red blood cell and plasma fatty acids.
Notes	Visual acuity and growth parameters given in Figures; investigators contacted for actual values but no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Carlson 1992 (Continued)

Random sequence generation (selection bias)	Unclear risk	Can't tell
Allocation concealment (selection bias)	Unclear risk	Method used for allocation concealment not clear
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up complete
Selective reporting (reporting bias)	Low risk	Yes
Other bias	Low risk	Yes

Carlson 1996

Methods	Randomised double-blind trial, single centre, Memphis. Intervention and outcome assessment were blinded. Follow-up was complete. Infants were randomised by sealed envelopes, stratified by gender.
Participants	94 infants were recruited and 59 completed study through to 4 months. Selection criteria included birthweight between 747 and 1275 g. More controls dropped out than supplemented infants and replacements were added to balance the groups. 40% of subjects had bronchopulmonary dysplasia (defined as an oxygen requirement for > 28 days) which is associated with impaired vision and development. Therefore, data are given for subgroups of infants with or without bronchopulmonary dysplasia. Supplemented group for visual acuity GA 28.5 ± 1.2 wk, BW 1069 ± 153 g no BPD & GA 27.0 ± 1.1 wk, BW 947 ± 130 g with BPD vs in control group GA 28.6 ± 1.3 wk, BW 1112 ± 106 g no BPD & GA 27.5 ± 1.6 wk, 975 ± 151 g. For the Fagan test of infant development, supplemented group GA 27.9 ± 1.5 wk, BW 1027 ± 153 g, n = 15 vs control GA 28.2 ± 1.5 wk, BW 1050 ± 149 g, n = 12.
Interventions	Supplemented formula fed from 3 to 5 days of age to 48 wk PCA. Supplemented formula 21.2% LA, 2.4% ALA, 0.06% EPA, 0.20% DHA vs control formula 21.2% LA, 2.4% ALA. All fed standard formula from 2 months' PCA to 12 months' PCA (34.3% LA, 4.8% ALA).
Outcomes	Visual acuity (Teller acuity cards), plasma fatty acids and growth (including normalised data). Fagan test of infant development were reported for a subset at 12 months.
Notes	Change of test format for infant development resulted in a smaller sample size than planned (sample size required n = 60, sample size assessed n = 27) — the authors comment on type 2 error resulting from the unplanned loss of power. Only the results from infants tested with the same version of the Fagan test used in their 1993 study were published and therefore available for the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Can't tell

Longchain polyunsaturated fatty acid supplementation in preterm infants (Review)

Carlson 1996 (Continued)

Allocation concealment (selection bias)	Low risk	Yes (sealed envelopes) Stratification by gender
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up complete
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Carnielli 2007

Methods	Randomised controlled trial, single centre, the Netherlands. Infants were randomised to 2 groups to receive supplemented or control formula. Method of randomisation and concealment of random allocation unclear. Blinding of intervention unclear. Outcome assessors were blinded. Follow-up complete (100 %).
Participants	Healthy preterm infants (n = 22), "normally growing", were randomised to supplemented or control formula. Specific health characteristics, age at enrolment, and milk and caloric intake are not reported. Exclusion criteria not reported. Gestational age and birth weight in LCPUFA vs control groups were 31.0 ± 2.0 wk vs 31.0 ± 2.0 wk, and 1.16 ± 0.27 kg vs 1.15 ± 0.36 kg, respectively).
Interventions	Infants in both groups were fed study formulae (80 kcal/100 mL) from enrolment until 7 months postnatal age. Composition of study formulae was nearly identical except for DHA and AA which were not present in control formula. Supplemented formula contained 0.64% DHA and 0.84% AA derived from single-cell oils.
Outcomes	Plasma phospholipid fatty acids, estimation of endogenous LCPUFA synthesis, weight at 7 months postnatal age.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Can't tell
Allocation concealment (selection bias)	Unclear risk	Can't tell
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: can't tell Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias)	Low risk	Follow-up complete

Longchain polyunsaturated fatty acid supplementation in preterm infants (Review)

Carnielli 2007 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Clandinin 1997

Methods	Randomised controlled study, single centre, Canada. Intervention and outcome assessments were blinded and all subjects were followed.
Participants	Medically stable preterm infants (n = 84), with AGA birth weights, who were receiving full enteral feeds by day 14 were randomised to control or one of three supplemented formulae. Infants were excluded or withdrawn (n = 18) if they received parenteral nutrition after 14 days of age, or they received steroids, red cell or plasma transfusions, or intravenous lipid after 8 days of age. 18 infants received the medium level LC PUFA supplement vs 18 the control formula (GA 31.9 ± 1.8 wk, BW 1.73 ± 0.44 kg vs GA 31.6 ± 2.3 wk, BW 1.74 ± 0.30 kg).
Interventions	The control formula contained 12.8% LA and 1.4% ALA. There were three supplemented formulae: low (0.32% AA & 0.24% DHA), medium (0.49% AA & 0.35% DHA) and high (1.1% AA & 0.76% DHA). The AA and DHA were obtained from single cell oils.
Outcomes	Fatty acids in erythrocyte membrane phospholipids, lymphocyte membrane phospholipids and plasma phospholipids were measured at 2 and 6 wk. Anthropometric measurements were recorded at birth, and at 2 and 6 wk of age. (6 wk measurement/38 weeks PMA entered as term data)
Notes	The formula-fed group receiving the medium level of LCPUFA supplementation had erythrocyte fatty acids similar to the breast milk-fed group and therefore are included as the comparison with controls for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Can't tell
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up complete
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Clandinin 2005

Methods	<p>Randomised, double-blinded, controlled trial, multicentre.</p> <p>Infants were randomised, stratified by birthweight (< 1000g, 1000 to 1500g, > 1500g), by computer-generated assignment schedules to receive control formula or one of two supplemented formulae. Interventions and assessors of outcomes were blinded. Follow-up was incomplete (50% to 60% for the primary outcome, 44% to 46% for neurodevelopment).</p>
Participants	<p>Preterm infants $\leq$ 35 weeks were eligible if they had received < 10 days of enteral feedings > 30 ml/kg/day. Exclusion criteria: GI tract and liver abnormalities and/or disease including confirmed NEC, congenital abnormalities or diseases likely to interfere with evaluation. 361 infants were enrolled. BW (GA): algal/fungal DHA group: 1189 ± 34 g (29.4 ± 0.3 wk), fish/fungal DHA group: 1107 ± 31 g (28.8 ± 0.2 wk), BW of the control group: 1215 ± 33 g (29.6 ± 0.3 wk). In addition, there was a non-randomised reference group of 105 breast-fed term infants.</p>
Interventions	<p>Infants were fed preterm formula from enrolment until near discharge (24 kcal/oz), discharge formula to 3 months post-term (22 kcal/oz), and term formula to 12 months post-term (20 kcal/oz). Each study group was provided with ready-to-use formulae, the only differences being the polyunsaturated fatty acid profiles due to absence of DHA and AA in control formula. There were 2 supplemented groups (algal/fungal oil or fish/fungal oil) and for the meta-analysis in this review, we chose the algal/fungal group because a) microbial oils are very similar to human milk fat and b) results of the trial suggested superiority of algal/fungal over fish/fungal oil for the primary outcome of the trial. The supplemented formulae contained either 17 mg/100 kcal algal DHA and 34 mg/100 kcal fungal AA or 17 mg/100 kcal fish DHA and 34 mg/100 kcal fungal AA. The preterm supplemented formulae contained 18.6% LA and 2.4% ALA, 0.33% algal DHA, 0.33% fungal DHA vs 18.7% LA and 2.4% ALA in the control formula.</p>
Outcomes	<p>Primary outcome was weight at 4 months and 12 months post-term. Secondary outcomes included several anthropometric measurements over the first 18 months, neurodevelopment assessed by Bayley Scales of Infant Development (MDI, PDI) at 18 months post-term, data on fluid intake, feeding tolerance and a range of blood tests (blood picture, cholesterol, glucose, tryglycerides, electrolytes and minerals, liver and kidney function tests), and adverse events.</p>
Notes	<p>Change of enrolment criteria during study. Initially infants > 1500 g were included in the study. After an amendment of the protocol, only infants $\leq$ 1500 g were enrolled. Authors provided numerical data for growth and neurodevelopmental outcome (these appeared only in Figures in the publication) as well as methodological details.</p> <p>This study was sponsored by Mead Johnson Nutritionals, Indiana, USA, who also provided the study formulae.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes (computer-generated randomisation schedules)
Allocation concealment (selection bias)	Low risk	Yes (using sealed opaque envelopes)
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up incomplete: Primary outcome of weight at 4 months and 12 months post-term: 50% to 60% Neurodevelopment: 44% to 46%

Clandinin 2005 (Continued)

Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Diersen-Schade 1998

Methods	Infants were randomised to receive control formula or 1 of 2 supplemented formulae. It is unclear whether assessment was blinded or whether follow up was complete.
Participants	Preterm infants (n = 194) with BW 0.86 to 1.56 kg.
Interventions	The supplemented formulae contained either 0.15% algal DHA or 0.14% algal DHA and 0.27% fungal AA. The LA:ALA ratio of the control formula is not available.
Outcomes	Anthropometric measurements and visual acuity (Teller acuity cards) were recorded at 2 and 4 months postconceptional age.
Notes	Abstract only is available. The formula supplemented with DHA and AA was compared with control formula for this review. There was a breast milk-fed reference group (n = 80). 194 infants were randomised. An assumption was made for this review that there were 64 per group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Can't tell
Allocation concealment (selection bias)	Unclear risk	Can't tell
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Can't tell
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Can't tell
Selective reporting (reporting bias)	Unclear risk	Can't tell
Other bias	Unclear risk	Can't tell

Fadella 1996

Methods	Randomised controlled trial, single centre, Italy. Infants were randomised on day 10 to supplemented or control formula. No allocation concealment and interventions were not blinded. It is not stated whether assessment of outcome was blinded. Follow-up of subjects is complete.
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Fadella 1996 (Continued)

Participants	Preterm AGA infants were included if > 50% nutrition was enteral on day 10. Supplemented group: GA 31.1 ± 1.2 wk, BW 1583 ± 310 g, n = 21. Control group: GA 31.3 ± 1.2 wk, 1463 ± 273 g, n = 25.
Interventions	Supplemented formula LA 10.8% to 12.2%, ALA 0.40% to 0.73%, DHA 0.23%, AA 0.23%. Control formula LA 18.6% to 19.4%, ALA 0.25% to 0.9%, DHA 0.01%, AA 0.02%.
Outcomes	At 52 weeks PCA, flash visual evoked potentials (VEP), electroretinograms (ERG) and auditory responses were measured. RBC total fatty acids were also measured.
Notes	66 infants were enrolled, 17 of whom formed a breast milk-fed reference group. The formula groups received up to 25% milk as breast milk. Methodology of assessment for VEP and ERG deviate from international standards and therefore interpretation is difficult.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Can't tell
Allocation concealment (selection bias)	High risk	No
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of intervention: no Blinding of outcome measurement: can't tell
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up complete
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	Formula groups received up to 25% of milk as breast milk Methodology of assessment of VEP and ERG deviate from international standards

Fang 2005

Methods	Double-blind randomised controlled trial, single centre, Taiwan. Infants were randomised by drawing lots, intervention was double blinded, assessors of outcomes were probably blinded, follow-up rate of neurodevelopmental assessment at 12 months was 81% to 94%.
Participants	Preterm AGA 30 to 37 wk were eligible if they had normal fundus oculi and had not been started on oral feeds. 27 infants (intervention group: n = 16, control group: n = 11) were enrolled. Supplemented group BW 1980 ± 110 g, GA 33.3 ± 0.5 wk. Control group BW 1990 ± 120 g, GA 33.0 ± 0.5 wk. Exclusion criteria: breastfeeding, maternal diabetes or drug abuse, sepsis, chronic lung disease, PVL, surgical NEC, administration of products containing DHA or AA, mechanical ventilation after introducing feeds, and various other conditions and diseases.

Fang 2005 (Continued)

Interventions	Supplemented formula ("Neoangelac Plus") LA/ALA 10:1, DHA 0.05% and AA 0.1% from unicellular organisms. Control formula ("Neoangelac") LA/ALA 10:1, no added DHA/AA. Study formula was given from reaching 32 wk postconceptional age and weight > 2000 g for 6 months.
Outcomes	Outcomes included neurodevelopment at 6 months and 12 months post-term (Bayley Scales of Infant Development (MDI, PDI)), anthropometric measurements at 1, 2, 3, 4, 5, 6, 12 months, and visual acuity by steady state VEP, Lea grating cards, and 'Hiding Heidi' low contrast cards at 4 and 6 months after enrolment.
Notes	Initially the authors planned to enrol 30 infants in each group, but because of increase in breastfeeding, strict exclusion criteria and an outbreak of SARS the number of included subjects was lower. Study formula was provided by Multipower Enterprise Corporation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably adequate (drawing lots)
Allocation concealment (selection bias)	Unclear risk	Method used for allocation concealment not clear
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rate of primary outcome 81% to 94%
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Fewtrell 2002

Methods	Double-blind randomised controlled trial, multicentre, UK. Infants were randomised, double-blind, stratified by birthweight (< & > 1200g), centre-wise in permuted blocks by independent personnel to receive supplemented or control formula. Assessment was blinded and follow-up was complete.
Participants	Preterm infants (n = 195) from 3 centres were included if BW < 1750g and fully formula fed by 10 days, and no congenital malformations. Supplemented group BW 1336 ± 284 g, GA 30.4 ± 2.3 wk. Control group BW 1353 ± 274 g, GA 30.3 ± 2.4 wk.
Interventions	Control preterm formula contained 10.6 % fa LA and 0.7% fa ALA. Supplemented preterm formula contained 0.17% fa DHA, 0.31% fa AA and 0.04% fa EPA. Trial formula was fed for a mean ± SD of 33 ± 17 days.
Outcomes	Primary outcome was neurodevelopment at 18 months post-term. Bayley Scales of Infant Development (MDI, PDI) at 18 months post-term. Knoblock, Passamanik & Sherrard's Developmental Screening Inventory at 9 months post-term. Neurological impairment at 9 and 18 months post-term. Growth in hospital and at 9 and 18 months post-term.

Fewtrell 2002 (Continued)

Notes

Funded by Numico Research BV (Wageningen, The Netherlands).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes
Allocation concealment (selection bias)	Low risk	Blinding of randomisation: yes Stratification by birth weight
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 80% follow-up. Neurodevelopment follow-up: at 9 months: 80/100 control & 78/95 intervention; at 18 months: 81/100 control & 69/95 intervention Growth follow-up: at 9 months: 80/100 control & 78/95 intervention; at 18 months: 84/100 control & 74/95 intervention
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Fewtrell 2004

Methods	Randomised, double-blinded trial, multicentre, UK. Infants were randomised, double-blind, stratified by birthweight (< & > 1200g), centre-wise in permuted blocks by independent personnel to receive supplemented or control formula. Outcome assessors were blinded and follow-up rate for the primary outcome was 87% and 80% in treatment and control group respectively.
Participants	Preterm infants (n = 238) from 5 UK centres were included if BW ≤ 2000 g and < 35 wk gestation if they received at least some of their enteral feeds as formula milk. They were enrolled when the attending paediatrician decided that infant formula should be started. Age at randomisation: supplemented group 14.3 ± 9.6 days. Control group 13.9 ± 10.4 days. Supplemented group BW 1487 ± 342 g, GA 31.2 ± 2.1 wk. Control group BW 1510 ± 326 g, GA 31.1 ± 1.9 wk. Exclusion criteria: congenital abnormalities known to affect growth or neurodevelopment.
Interventions	Infants were fed preterm formula until the infant reached 2 kg or was discharged. After this point, post-discharge (nutrient-enriched) formula was given. Control preterm formula contained 11.5 % LA and 1.6 % ALA. Supplemented preterm formula contained 12.3 % LA, 1.5 % ALA, 0.5 % DHA, 0.9% C18:3 n-6 gamma-LA, 0.04 % AA and 0.1 % EPA (borage/fish oil) . Formula was given from enrolment to 9 months post term.
Outcomes	Primary outcome was neurodevelopment at 18 months post-term. Bayley Scales of Infant Development (MDI, PDI) at 18 months post-term. Knoblock, Passamanik & Sherrard's Developmental Screening Inventory at 9 months post-term. Neurological impairment at 9 and 18 months post-term. Growth in hospital and at 9 and 18 months post-term. Adverse events.

Fewtrell 2004 (Continued)

Notes Supported by a grant from H. J. Heinz Company who also provided the study formulas.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes. Infants were randomised, double-blind, stratified by birthweight (< & > 1200g), centre-wise in permuted blocks by independent personnel to receive supplemented or control formula.
Allocation concealment (selection bias)	Low risk	Yes "dietary allocations stored in sealed opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rate of primary outcome 80% to 87%
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Groh-Wargo 2005

Methods	<p>Double blind, randomised, controlled study, multicentre, USA.</p> <p>Infants were randomised, double-blind, to 3 groups based on gender and stratified by birth weight (750 to 1250 g/1251 to 1800 g) in permuted blocks to receive supplemented or control formula. Intervention was blinded. Outcome assessors were blinded. Follow-up rate of anthropometrics at 4 months was 92% and 77% in treatment and control group respectively. Follow-up rate at 12 months was 77% in both treatment and control group.</p>
Participants	<p>40 infants < 33 wk gestation and between 750 and 1800 g birth weight and < 28 days (control n = 13, fungal/fish n = 13, egg-TG/fish N = 14). Supplemented groups: fungal/fish: BW 1424 ± 331 g, GA 30.6 ± 2.5 wk; egg/fish: BW 1367 ± 242 g, GA 30.4 ± 2.1 wk; control group BW 1322 ± 270 g, GA 30.0 ± 2.3 wk. Exclusions include serious congenital malformations, major surgery, asphyxia, PVL and IVH > grade 2 and serious systemic infection.</p>
Interventions	<p>Infants were fed preterm formula until term-corrected age then post-discharge nutrient-enriched formula until 12 months post-term. There were two supplemented groups (fungal/fish oil or egg-TG/fish oil) and, for this meta-analysis and review, we chose the fungal/fish group as microbial oils are more similar to human milk fat than egg-TG. Supplemented formula contained 0.42% AA and 0.27% DHA until term, and then 0.42% AA and 0.16% DHA until 12 months. Control formula contained 16% to 19% LA and 2.5% ALA. Infants in all groups also received human milk, for example at term, 33% control and 50% supplemented infants consumed human milk at least once per day.</p>
Outcomes	<p>Primary outcome was body composition as measured by absorptiometric x-ray techniques (DEXA) at 4 months post-term. Other outcomes included body composition and anthropometrics at 35 wk and 40 wk corrected age, 4 months and 12 months post-term. Biochemical outcomes included blood fatty acid profiles.</p>

Groh-Wargo 2005 (Continued)

Notes 20 of the 60 participants of this study are already included in the multicentre trial [O'Connor 2001](#). The authors clarified methodological details and provided anthropometric raw data of the 40 infants who were not included in [O'Connor 2001](#).
The study was supported by a grant from Ross Products Division, Abbott Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants were randomised, double-blind, to 3 groups based on gender and stratified by birth weight (750 to 1250 g/1251 to 1800 g) in permuted blocks to receive supplemented or control formula.
Allocation concealment (selection bias)	Low risk	Yes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rate of primary outcome of body composition at 4 months post-term: 77% to 92% Follow-up rate at 12 months post-term: 77%
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Innis 2002

Methods	Double-blind randomised controlled study, multicentre, North America. Double-blind prospective randomised trial (blinding of assessment unclear). Infants randomised to 1 of 3 formulae by computer-generated randomisation schedules. 2 different codes were used for each of the formulae to ensure blinding. Follow-up was complete.
Participants	194 healthy preterm infants BW 846 to 1560 g. Exclusion: small for gestational age, > 24 days of age when full enteral feeds tolerated, NEC or other GI disease, impaired vision, disease/congenital malformation that may impair growth. Supplemented GA 29.7 ± 1.7 wk, BW 1.28 ± 0.18 g, n = 66. Control GA 29.5 ± 1.7 wk, BW 1.23 ± 0.18 g, n = 62.
Interventions	There were 3 preterm formulas: control (21% to 22% LA, 3% to 3.1% ALA); 2 supplemented (0.34% DHA from DHA-enriched oil, or 0.33% DHA and 0.60% AA from algal/fungal oils; neither had EPA). For this meta-analysis and review, we chose the supplement with DHA and AA. Formulae were fed from when 50 kcal/kg/d was tolerated, for at least 28 days until discharge. Term formula without DHA and AA was fed after discharge.
Outcomes	RBC fatty acids at discharge and 48 wk PMA. Anthropometrics at 40, 48 and 57 wk PMA. Visual acuity (Teller acuity cards) at 48 and 57 wk PMA.
Notes	Sponsored by Mead Johnson Nutritionals, Indiana.

Risk of bias

Innis 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes (computer-generated randomisation schedules)
Allocation concealment (selection bias)	Unclear risk	Method used for allocation concealment not clear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of intervention: yes Blinding of outcome measurement: can't tell
Incomplete outcome data (attrition bias) All outcomes	Low risk	173/194 "completed the premature formula feeding phase" "All infants with available data were included in the analysis of result". For growth, lowest follow-up was 77%. For visual acuity, follow-up rates were: 51/62 control & 57/66 DHA + ARA at 48 weeks and 46/62 control & 55/66 DHA + ARA at 57 weeks
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Lapillonne 2000

Methods	Infants were randomised, double-blind, to 2 groups to receive supplemented or control formula. Allocation was concealed using sealed opaque envelopes. Intervention was blinded. Outcome assessors were blinded. Follow-up rate of anthropometrics at 3 months and 6 months post-term was 100%.	
Participants	23 healthy preterm infants, BW 700 to 1500 g. Exclusion: major neonatal morbidity (e.g. congenital malformations, respiratory treatment for more than 10 days, congenital infection, NEC, bowel resection), postnatal age > 21 days, supplemental oxygen, or treatments that could influence growth and development (e.g. diuretics or corticosteroids), failure to achieve full enteral feeds (150 ml/kg/d) by 21 days of life, maternal history of substance abuse, diabetes, hyperlipidaemia, or abnormal dietary patterns (strict vegetarian diet). Supplemented GA 29.4 ± 1.4 wk, BW 1.28 ± 0.17 kg, n = 11. Control GA 29.7 ± 1.7 wk, BW 1.24 ± 0.16 kg, n = 12.	
Interventions	Enteral feeding of all infants was started during the first week of life using pooled, pasturized breast milk. Formula feeding began during the first 3 weeks of life if mothers had decided not to breast feed. Infants were fed preterm formula from enrolment until term-corrected age. After this point, term formula was given until 4 months post-term. Control preterm formula contained 18.0% LA and 1.6% ALA. Supplemented preterm formula contained 17.8% LA, 1.1% ALA, 0.37% DHA, 0.02% AA and 0.05% EPA (LCPUFA from fish oil).	
Outcomes	RBC fatty acids and anthropometrics at enrolment, discharge, term-corrected age, 3 and 6 months post-term. Primary outcome was RBC DHA content.	
Notes	This study also reported on a non-randomised control group of breast-fed infants (n = 10) who are not subject of this review.	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Lapillonne 2000 (Continued)

Random sequence generation (selection bias)	Low risk	Yes
Allocation concealment (selection bias)	Low risk	Yes (using sealed envelopes)
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up complete
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

O'Connor 2001

Methods	Double-blind, randomised controlled study, multicentre, UK and North America. Infants were randomised to 3 groups based on centre, gender, BW stratified 750 to 1250 g and 1251 to 1800 g. Infants were enrolled from 8 centres in UK and North America. It is assumed that the study was double-blind but this is not clearly stated. Assessment was blinded and follow-up was complete.
Participants	470 infants < 33 wk gestation and between BW 750 and 1805 g and < 28 days age (control n = 144, fungal/fish n = 140, egg-TG/fish N = 143, human milk exclusively n = 43). Exclusions include serious congenital malformations, major surgery, asphyxia, PVL and IVH > grade 2 and serious systemic infection. Supplemented group BW 1305 ± 293.
Interventions	Infants fed preterm formula until term corrected age then post-discharge (nutrient-enriched) formula until 12 months post-term. There were 2 supplemented groups (fish/fungal oil or egg-TG/fish oil) and, for this meta-analysis and review, we chose the fish/fungal group as microbial oils are more similar to human milk fat than egg-TG, and there were minimal differences between fish/fungal and egg-TG/fish groups. Supplemented formula contained 0.42% AA and 0.26% DHA until term, and then 0.42% AA and 0.16% DHA until 12 months. Control formula contained 16% to 19% LA and 2.5% ALA. Infants in all groups also received human milk, for example at term, 35% control and 28% supplemented infants consumed human milk at least once per day.
Outcomes	Primary outcome was Bayley Scales of Infant development at 12 months. Visual acuity was assessed by Teller acuity cards at 2, 4 and 6 months' corrected age, and by VEP in 2/8 centres at 4 and 6 months' corrected age. Fagan test of Infant Intelligence was administered at 6 and 9 months' corrected age. MacArthur Communicative Development Inventories was administered at 9 and 14 months' corrected age. Growth was measured at term and 2, 4, 6, 9 and 12 months.
Notes	Sponsored by Ross Products Division, Abbott Laboratories, Ohio. Authors contacted to provide data for growth and visual acuity, as these appear only in Figures in the publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
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O'Connor 2001 (Continued)

Random sequence generation (selection bias)	Low risk	Yes
Allocation concealment (selection bias)	Low risk	Yes Stratification by gender and birth weight
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	80% of the enrolled infants completed the study to 12 months' corrected age.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Uauy 1990

Methods	Outcome assessment was blinded but it is not stated whether randomisation and intervention were blinded. Follow-up of subjects was complete.
Participants	Supplemented group GA 30.7 ± 1.2 wk, BW 1281 ± 101 g. Control groups a) GA 30.9 ± 1.6 wk, BW 1340 ± 106 g, b) GA 29.6 ± 1.6 wk, BW 1224 ± 92 g.
Interventions	Infants were fed study formulae, on average, from day 10 to day 45. Infants were randomised to the supplemented group who received soy/marine oil (LA 20.4%, ALA 1.4%, n-6 0.1%, n-3 1.0%) or control group a) corn oil (LA 24.2%, ALA 0.5%) or control group b) soy oil (LA 20.8%, ALA 2.7%).
Outcomes	ERG at 36 wk and 57 wk PCA. VEP acuity at 36 & 57 wk PCA. FPL acuity at 57 wk PCA. Lipid peroxidation products (TBARS) or thiobarbituric acid reactive substances expressed as -azide/+azide × 100% which normalises for individual variation, high % suggests a high capacity for lipid peroxidation. Infant bleeding times 57 wk PCA. RBC membrane fluidity at 25 and 37 degrees. Growth at 40 wk, 48 wk and 57 wk PCA.
Notes	For the purpose of this analysis, control group b) was used as the LA:ALA ratio is most similar to other studies and current commercial formula.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Can't tell
Allocation concealment (selection bias)	Unclear risk	Method used for allocation concealment not clear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: can't tell Blinding of outcome measurement: yes

Uauy 1990 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rate of 95% (42/44).
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

van Wezel 2002

Methods	Double-blind, randomised controlled study, single centre, Sweden. Double-blind study with complete follow-up. Infants were randomised using computer-generated random list and applied by an independent research officer. Assessment was blinded and follow up was complete.	
Participants	Preterm infants (< 34 wk GA and < 1750 g). Supplemented group BW 1.282 ± 0.316 kg, GA 30.4 ± 1.5 wk, n = 22. Control group BW 1.30 ± 0.257 g, GA 30.4 ± 1.6 wk, n = 20. Inclusion criteria: normal neurological examination and cerebral ultrasounds. Exclusion criteria: significant cerebral damage, retinopathy, chronic disease or feeding problems.	
Interventions	Supplemented preterm and term formula contained 0.34% DHA and 0.68% AA from micro algae. LA and ALA levels are not given. Preterm formula was fed until a weight of 3 kg. Infants then received a term formula with or without supplement as per randomisation until 6 months' corrected age.	
Outcomes	Cerebral myelination assessed by magnetic resonance imaging (MRI). Bayley Scales of Infant Development (MDI, PDI), visual acuity by flash VEP and Teller cards, RBC and plasma fatty acids.	
Notes	Sponsored by Nutricia, Numico Research.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes (computer-generated randomisation schedules)
Allocation concealment (selection bias)	Low risk	Yes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up complete
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Vanderhoof 1999

Methods	Randomisation computerised and stratified by BW (750 to 1000 g, 1001 to 1500 g, 1501 to 2000 g). Blinding by coded labels and verified by "trained sensory panel". It is unclear whether assessment was blinded. Follow-up was complete.
Participants	Supplemented group BW 1522 ± 370 g, GA 31.0 ± 2.5 wk, n = 77. Control group BW 1484 ± 365 g, GA 30.8 ± 2.7 , n = 78. Inclusion criteria: preterm BW 750 to 2000 g, 0 to 28 days of age, medically stable, received enteral feeds for < 24 h, AGA. Exclusion criteria: significant acute/chronic illness, systemic infections, major congenital malformations, IVH > grade 2, PVL, seizures. Withdrawal criteria: if BW > 1000g and full enteral feeds not attained by day 28; if BW 750 to 1000 g and full enteral feeds not attained by day 42; for all infants, if unable to tolerate full enteral feeds; or need for mechanical ventilation after full enteral feeds attained; or oxygen dependency at 36 wk PCA; and/or > 5-day course steroids. Infants enrolled from 16 sites.
Interventions	Supplemented preterm formula LA 12.1% fa, ALA 1.5% fa, AA 0.50% fa and DHA 0.35% (LCPUFA from single cell oil source). Control preterm formula LA 12.8% fa, ALA 1.4% fa, AA and DHA 0%. Infants were fed 1 of 2 preterm formulas, with or without LCPUFA, until 48 weeks PCA. All infants were then fed a standard term formula (un-supplemented) until 92 wk PCA.
Outcomes	Anthropometrics, adverse events and plasma fatty acids were measured to 92 wk PCA.
Notes	Sponsored by Wyeth Nutritionals International, Philadelphia, Pennsylvania, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes (computer-generated randomisation schedules)
Allocation concealment (selection bias)	Low risk	Yes (coded labels) Stratification by birth weight
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of intervention: yes Blinding of outcome measurement: can't tell
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow up complete.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

AA = arachidonic acid
 AGA = appropriate for gestational age
 ALA = alpha linolenic acid
 BW = birth weight
 DHA = docosahexaenoic acid
 EPA = eicosapentaenoic acid
 ERG = electroretinogram
 fa = fatty acid
 g = gram(s)
 GA = gestational age
 h = hour(s)

IVH = intraventricular haemorrhage

LA = linoleic acid

NEC = necrotizing enterocolitis

PCA = postconceptional age

PVL = periventricular leukomalacia

RBC = red blood cell

wk = week(s)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Almaas 2015	Preterm infants in the intervention and control arm received human milk. It was not a RCT comparing LCPUFA versus no LCPUFA-supplemented formula milk in preterm infants.
Alshweki 2015	Compared effects of formula containing different ratios of LCPUFA (2:1 AA:DHA (omega-6: omega-3) ratio to 1:1 AA:DHA ratio in preterm infants < 1500g and/or between 25 to 32 weeks' gestational age. It was not a RCT comparing LCPUFA versus no LCPUFA-supplemented formula milk in preterm infants.
Baack 2016	Compared effects of enteral DHA supplementation (50mg/day) in addition to standard nutrition for preterm infants. Outcome measure was blood fatty acid levels, not clinical outcomes.
Collins 2010	Reported the effect of higher-dose DHA supplementation compared with standard DHA on growth in infants who participated in the DINO trial (infants born < 33 weeks' gestation). It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
Collins 2011	Reported the effect of higher-dose DHA on growth of pre-term infants receiving breast milk and/or formula to 18 months CA compared to standard feeding practice. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
Collins 2015	Follow up at 7 years' corrected age of infants who participated in the DINO RCT. Determined if improvements in cognitive outcome detected at 18 months' corrected age in infants born < 33 weeks' gestation receiving a high DHA compared with standard DHA diet were sustained in early childhood. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
Donzelli 1996	This was an RCT but published only in abstract form (conference proceedings). Data were inadequate to assess this study.
Koletzko 2003	This randomised study measured anthropometric data and fatty acid profiles within the study period of 28 days. The study was excluded because there were no follow-up data beyond 28 days.
Lim 2002	This was an RCT but published only in abstract form (conference proceedings). Data were inadequate to assess this study.
Makrides 2009	Compared neurodevelopmental outcome of preterm infants fed high-dose DHA to standard dose DHA. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
Rodriguez 2003	This trial compared LCPUFA supplemented formula with breast feeding and was not randomised. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
Shah 2009	Review article summarising Cochrane review of LCPUFA in term and preterm infants.
Smithers 2008b	Compared visual responses of preterm infants fed human milk and formula with high DHA concentration to standard DHA concentration. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.

Study	Reason for exclusion
Smithers 2008a	Determined the effect of increasing the DHA concentration of human milk and formula on circulating fatty acids of preterm infants. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
Smithers 2010	Follow up of DINO (DHA for the improvement of neurodevelopmental outcome in preterm infants) trial. Evaluated the effect of higher-DHA milk on behaviour and language development in early childhood. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.
van de Lagemaat 2011	Determined associations between growth and erythrocyte(RBC) DHA and AA in preterm infants. It was not a RCT comparing LCPUFA-supplemented versus unsupplemented formula milk.

DATA AND ANALYSES

Comparison 1. Supplement vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity (log cycles/degree) at term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 no BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Visual acuity (log cycles/degree) at 2 months post-term	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 no BPD	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Visual acuity (log cycles/degree) at 4 months post-term	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 no BPD	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Visual acuity (log cycles/degree) at 6 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 no BPD	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Visual acuity (log cycles/degree) at 9 months post-term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 no BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Visual acuity (log cycles/degree) at 12 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 no BPD	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 BPD	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Rod ERG at 36 wk PCA	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 log threshold (scot td-sec)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 log Vmax (uV)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 ERG at 3 months post-term, amplitude (uV)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Rod ERG at 4 months post-term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 log threshold (scot td-sec)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 log Vmax (uV)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 VEP at 3 months post-term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 N4 latency (millisec)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 P4 latency (millisec)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Fagan infant test at 12 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 novelty time (% total time)	2	84	Mean Difference (IV, Fixed, 95% CI)	-4.11 [-7.47, -0.76]
11.2 total looks (n)	2	84	Mean Difference (IV, Fixed, 95% CI)	5.52 [2.16, 8.87]
11.3 time/look (sec)	2	84	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.21, 0.02]
12 Fagan infant test at 9 months post-term (% total time)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 novelty time (%)	2	232	Mean Difference (IV, Fixed, 95% CI)	0.42 [-1.40, 2.24]
12.2 total looks (n)	1	51	Mean Difference (IV, Fixed, 95% CI)	7.20 [2.49, 11.91]
12.3 time/look (sec)	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.29, 0.03]
13 Bayley MDI at 12 months post-term	4	364	Mean Difference (IV, Fixed, 95% CI)	0.96 [-1.42, 3.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Bayley PDI at 12 months post-term	4	353	Mean Difference (IV, Fixed, 95% CI)	0.23 [-2.77, 3.22]
15 Weight at 6 wk post-term (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16 Length at 6 wk post-term (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17 Head circumference at 6 wk post-term (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18 Weight at term (kg)	4	296	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.16]
19 Length at term (cm)	4	295	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.27, 0.96]
20 Head circ at term (cm)	3	185	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.26, 0.62]
21 Weight at 2 months post-term (kg)	5	485	Mean Difference (IV, Fixed, 95% CI)	0.21 [0.08, 0.33]
22 Length at 2 months post-term (cm)	4	297	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.00, 0.94]
23 Head circumference at 2 months post-term (cm)	3	187	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.33, 0.38]
24 Growth rate until 3 months post-term	1	138	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.04, 0.04]
24.1 weight g/d	1	46	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.56, 2.36]
24.2 length cm/w	1	46	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.06, 0.06]
24.3 head circumference cm/w	1	46	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.06, 0.06]
25 Weight at 4 months post-term (kg)	6	489	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.01, 0.29]
26 Length at 4 months post-term (cm)	5	299	Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.22, 0.84]
27 Head circumference at 4 months post-term (cm)	4	198	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.48, 0.30]
28 Weight at 12 months post-term (kg)	4	271	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.31, 0.12]
29 Length at 12 months post-term (cm)	4	271	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.33, 0.84]
30 Head circumference at 12 months post-term (cm)	4	271	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.53, 0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31 Normalised weight at 12 months post-term	2	116	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.56, -0.09]
32 Normalised length at 12 months post-term	2	116	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.16, 0.22]
33 Normalised head circumference at 12 months post-term	2	116	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.38, 0.10]
34 Lipid peroxidation (TBARS -azide/+azide x 100%), 4 months post-term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
35 RBC fragility (hemolysis with 8% to 10% H2O2) , 4 months post-term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
36 Infant bleeding time 4 months post-term (ped device, min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
37 Bayley MDI at 18 months post-term	3	494	Mean Difference (IV, Fixed, 95% CI)	2.40 [-0.33, 5.12]
38 Bayley PDI at 18 months post-term	3	496	Mean Difference (IV, Fixed, 95% CI)	0.74 [-1.90, 3.37]
39 KPS Developmental Screening Inventory at 9 months post-term (overall quotient)	1	158	Mean Difference (IV, Fixed, 95% CI)	1.50 [-1.70, 4.70]
40 Weight at 9 months post-term	2	374	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.22, 0.21]
41 Length at 9 months post-term	2	374	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.58, 0.61]
42 Head circumference at 9 months post-term	2	374	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.37, 0.30]
43 Normalised weight at 9 months post-term	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.72, 0.02]
44 Normalised length at 9 months post-term	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.3 [-0.69, 0.09]
45 Normalised head circumference at 9 months post-term	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.51, 0.31]
46 Weight at 18 months post-term	2	396	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.39, 0.10]
47 Length at 18 months post-term	2	396	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.91, 0.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
48 Head circumference at 18 months post-term	2	396	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.53, 0.18]
49 Normalised weight at 18 months post-term	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.68, 0.02]
50 Normalised length at 18 months post-term	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.80, -0.08]
51 Normalised head circumference at 18 months post-term	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.52, 0.32]
52 Fagan Infant test at 6m post-term, novelty time (%total time)	1	187	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.64, 1.64]
53 MacArthur Communicative Inventories at 14 months post-term	1	399	Mean Difference (IV, Fixed, 95% CI)	0.34 [-3.05, 3.72]
53.1 vocab comprehension scores	1	199	Mean Difference (IV, Fixed, 95% CI)	1.70 [-2.96, 6.36]
53.2 vocab production scores	1	200	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-6.14, 3.74]
54 Bayley MDI at 24 months post-term	1	42	Mean Difference (IV, Fixed, 95% CI)	4.10 [-8.06, 16.26]
55 Bayley PDI at 24 months post-term	1	42	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-12.11, 4.91]
56 Weight at 10 years	1	107	Mean Difference (IV, Fixed, 95% CI)	2.30 [-1.45, 6.06]
56.1 boys	1	51	Mean Difference (IV, Fixed, 95% CI)	-1.43 [-7.08, 4.22]
56.2 girls	1	56	Mean Difference (IV, Fixed, 95% CI)	5.26 [0.23, 10.29]
57 Height at 10 years	1	107	Mean Difference (IV, Fixed, 95% CI)	2.38 [-0.27, 5.03]
57.1 boys	1	51	Mean Difference (IV, Fixed, 95% CI)	0.0 [-4.43, 4.43]
57.2 girls	1	56	Mean Difference (IV, Fixed, 95% CI)	3.70 [0.39, 7.01]
58 Head circumference at 10 years	1	107	Mean Difference (IV, Fixed, 95% CI)	0.43 [-0.32, 1.17]
58.1 boys	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.65, 0.65]
58.2 girls	1	56	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.12, 2.08]

Analysis 1.1. Comparison 1 Supplement vs control, Outcome 1 Visual acuity (log cycles/degree) at term.

Analysis 1.2. Comparison 1 Supplement vs control, Outcome 2 Visual acuity (log cycles/degree) at 2 months post-term.

Analysis 1.3. Comparison 1 Supplement vs control, Outcome 3 Visual acuity (log cycles/ degree) at 4 months post-term.

Analysis 1.4. Comparison 1 Supplement vs control, Outcome 4 Visual acuity (log cycles /degree) at 6 months post-term.

Analysis 1.5. Comparison 1 Supplement vs control, Outcome 5 Visual acuity (log cycles/degree) at 9 months post-term.

Analysis 1.6. Comparison 1 Supplement vs control, Outcome 6 Visual acuity (log cycles/degree) at 12 months post-term.

Analysis 1.7. Comparison 1 Supplement vs control, Outcome 7 Rod ERG at 36 wk PCA.

Analysis 1.8. Comparison 1 Supplement vs control, Outcome 8 ERG at 3 months post-term, amplitude (uV).

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Fadella 1996	21	14.8 (4.6)	25	16 (6.8)		-1.2[-4.51,2.11]
					Favors suppl	Favors control

Analysis 1.9. Comparison 1 Supplement vs control, Outcome 9 Rod ERG at 4 months post-term.

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.9.1 log threshold (scot td-sec)						
Uauy 1990	14	-1.3 (0.3)	17	-1.4 (0.3)		0.03[-0.16,0.22]
1.9.2 log Vmax (uV)						
Uauy 1990	14	2.1 (0.2)	17	2.1 (0.1)		-0.04[-0.14,0.06]
					favours suppl	favours control

Analysis 1.10. Comparison 1 Supplement vs control, Outcome 10 VEP at 3 months post-term.

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.10.1 N4 latency (millisec)						
Fadella 1996	14	143 (17.4)	10	171 (20.8)		-28[-43.79,-12.21]
1.10.2 P4 latency (millisec)						
Fadella 1996	17	178 (22.7)	10	202 (19.4)		-24[-40.16,-7.84]
					Favors suppl	Favors control

Analysis 1.11. Comparison 1 Supplement vs control, Outcome 11 Fagan infant test at 12 months post-term.

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.11.1 novelty time (% total time)							
Carlson 1992	28	60.5 (6.9)	29	64.6 (6.5)		93.65%	-4.1[-7.57,-0.63]
Carlson 1996	15	59.7 (6.5)	12	64 (22.8)		6.35%	-4.3[-17.61,9.01]
Subtotal ***	43		41			100%	-4.11[-7.47,-0.76]
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P=0.98); I ² =0%							
Test for overall effect: Z=2.4(P=0.02)							
1.11.2 total looks (n)							
Carlson 1992	28	47.7 (7.4)	29	42.4 (7)		80.32%	5.3[1.56,9.04]
Carlson 1996	15	46.8 (10.5)	12	40.4 (9.6)		19.68%	6.4[-1.16,13.96]
Subtotal ***	43		41			100%	5.52[2.16,8.87]
Heterogeneity: Tau ² =0; Chi ² =0.07, df=1(P=0.8); I ² =0%							
Test for overall effect: Z=3.22(P=0)

Analysis 1.12. Comparison 1 Supplement vs control, Outcome 12 Fagan infant test at 9 months post-term (% total time).

Analysis 1.13. Comparison 1 Supplement vs control, Outcome 13 Bayley MDI at 12 months post-term.

Analysis 1.14. Comparison 1 Supplement vs control, Outcome 14 Bayley PDI at 12 months post-term.

Analysis 1.15. Comparison 1 Supplement vs control, Outcome 15 Weight at 6 wk post-term (kg).

Analysis 1.16. Comparison 1 Supplement vs control, Outcome 16 Length at 6 wk post-term (cm).

Analysis 1.17. Comparison 1 Supplement vs control, Outcome 17 Head circumference at 6 wk post-term (cm).

Analysis 1.18. Comparison 1 Supplement vs control, Outcome 18 Weight at term (kg).

Analysis 1.19. Comparison 1 Supplement vs control, Outcome 19 Length at term (cm).

Analysis 1.20. Comparison 1 Supplement vs control, Outcome 20 Head circ at term (cm).

Analysis 1.21. Comparison 1 Supplement vs control, Outcome 21 Weight at 2 months post-term (kg).

Analysis 1.22. Comparison 1 Supplement vs control, Outcome 22 Length at 2 months post-term (cm).

Analysis 1.23. Comparison 1 Supplement vs control, Outcome 23 Head circumference at 2 months post-term (cm).

Analysis 1.24. Comparison 1 Supplement vs control, Outcome 24 Growth rate until 3 months post-term.

Analysis 1.25. Comparison 1 Supplement vs control, Outcome 25 Weight at 4 months post-term (kg).

Analysis 1.26. Comparison 1 Supplement vs control, Outcome 26 Length at 4 months post-term (cm).

Analysis 1.27. Comparison 1 Supplement vs control, Outcome 27 Head circumference at 4 months post-term (cm).

Analysis 1.28. Comparison 1 Supplement vs control, Outcome 28 Weight at 12 months post-term (kg).

Analysis 1.29. Comparison 1 Supplement vs control, Outcome 29 Length at 12 months post-term (cm).

Analysis 1.30. Comparison 1 Supplement vs control, Outcome 30 Head circumference at 12 months post-term (cm).

Analysis 1.31. Comparison 1 Supplement vs control, Outcome 31 Normalised weight at 12 months post-term.

Analysis 1.32. Comparison 1 Supplement vs control, Outcome 32 Normalised length at 12 months post-term.

Analysis 1.33. Comparison 1 Supplement vs control, Outcome 33 Normalised head circumference at 12 months post-term.

Analysis 1.34. Comparison 1 Supplement vs control, Outcome 34 Lipid peroxidation (TBARS -azide/+azide x 100%), 4 months post-term.

Analysis 1.35. Comparison 1 Supplement vs control, Outcome 35 RBC fragility (hemolysis with 8% to 10% H2O2), 4 months post-term.

Analysis 1.36. Comparison 1 Supplement vs control, Outcome 36 Infant bleeding time 4 months post-term (ped device, min).

Analysis 1.37. Comparison 1 Supplement vs control, Outcome 37 Bayley MDI at 18 months post-term.

Analysis 1.38. Comparison 1 Supplement vs control, Outcome 38 Bayley PDI at 18 months post-term.

Analysis 1.39. Comparison 1 Supplement vs control, Outcome 39 KPS Developmental Screening Inventory at 9 months post-term (overall quotient).

Analysis 1.40. Comparison 1 Supplement vs control, Outcome 40 Weight at 9 months post-term.

Analysis 1.41. Comparison 1 Supplement vs control, Outcome 41 Length at 9 months post-term.

Analysis 1.42. Comparison 1 Supplement vs control, Outcome 42 Head circumference at 9 months post-term.

Analysis 1.43. Comparison 1 Supplement vs control, Outcome 43 Normalised weight at 9 months post-term.

Analysis 1.44. Comparison 1 Supplement vs control, Outcome 44 Normalised length at 9 months post-term.

Analysis 1.45. Comparison 1 Supplement vs control, Outcome 45 Normalised head circumference at 9 months post-term.

Analysis 1.46. Comparison 1 Supplement vs control, Outcome 46 Weight at 18 months post-term.

Analysis 1.47. Comparison 1 Supplement vs control, Outcome 47 Length at 18 months post-term.

Analysis 1.48. Comparison 1 Supplement vs control, Outcome 48 Head circumference at 18 months post-term.

Analysis 1.49. Comparison 1 Supplement vs control, Outcome 49 Normalised weight at 18 months post-term.

Analysis 1.50. Comparison 1 Supplement vs control, Outcome 50 Normalised length at 18 months post-term.

Analysis 1.51. Comparison 1 Supplement vs control, Outcome 51 Normalised head circumference at 18 months post-term.

Analysis 1.52. Comparison 1 Supplement vs control, Outcome 52 Fagan Infant test at 6m post-term, novelty time (%total time).

Analysis 1.53. Comparison 1 Supplement vs control, Outcome 53 MacArthur Communicative Inventories at 14 months post-term.

Analysis 1.54. Comparison 1 Supplement vs control, Outcome 54 Bayley MDI at 24 months post-term.

Analysis 1.55. Comparison 1 Supplement vs control, Outcome 55 Bayley PDI at 24 months post-term.

Analysis 1.56. Comparison 1 Supplement vs control, Outcome 56 Weight at 10 years.

Analysis 1.57. Comparison 1 Supplement vs control, Outcome 57 Height at 10 years.

Analysis 1.58. Comparison 1 Supplement vs control, Outcome 58 Head circumference at 10 years.

APPENDICES

Appendix 1. Central Register of Controlled Trials (CENTRAL) search strategy (searched 28/02/16)

#1 MESH descriptor: [Fatty Acids, Unsaturated] explode all trees

#2 MESH descriptor: [Lipids] explode all trees

#3 "longchain polyunsaturated fatty acid" or "long chain polyunsaturated fatty acid" or "LCPUFA"

#4 "polyunsaturated fatty acid" or "PUFA"

#5 "fish oil" or "marine oil" or "algal oil"

#6 "docosahexaenoic acid" or "DHA"

#7 "arachidonic acid"

#8 "eicosapentaenoic acid" or "EPA"

#9 lipid

#10 "omega-3" or "omega-6"

#11 "linoleic acid" or "linolenic acid"

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor: [Infant, Low Birth Weight] explode all trees

#14 MeSH descriptor: [Infant, Premature] explode all trees

#15 "small for gestational age"

#16 "low birthweight" or "low birth weight" or lbw

#17 preterm or "pre term" or premature

#18 #13 OR #14 OR #15 OR #16 OR #17

#19 #12 and #18

Appendix 2. MEDLINE (OvidSP) search strategy (searched 28/02/16)

1 exp Fatty Acids, Unsaturated/

2 exp Lipids/

3 (longchain polyunsaturated fatty acid* or long chain polyunsaturated fatty acid* or LCPUFA).tw.

- 4 (polyunsaturated fatty acid* or PUFA).tw.
- 5 (fish oil* or marine oil* or algal oil*).tw.
- 6 (docosahexaenoic acid* or DHA).tw.
- 7 arachidonic acid*.tw.
- 8 (eicosapentaenoic acid* or EPA).tw.
- 9 lipid*.tw.
- 10 (omega-3 or omega-6).tw.
- 11 (linoleic acid* or linolenic acid*).tw.
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 exp Infant, Low Birth Weight/
- 14 exp Infant, Premature/
- 15 (small adj2 gestational age).tw.
- 16 ((low adj1 birthweight) or (low adj1 birth weight)).tw.
- 17 (preterm or pre-term or prematur* or lbw).tw.
- 18 15 or 16 or 17
- 19 (infan* or newborn* or neonate*).tw.
- 20 18 and 19
- 21 13 or 14 or 20
- 22 randomized controlled trial.pt.
- 23 controlled clinical trial.pt.
- 24 randomi?ed.ab.
- 25 placebo.ab.
- 26 randomly.ab.
- 27 trial.ab.
- 28 exp Clinical Trials as Topic/
- 29 22 or 23 or 24 or 25 or 26 or 27 or 28
- 30 exp animals/ not humans.sh.
- 31 29 not 30
- 32 12 and 21 and 31

Appendix 3. Embase (OvidSP) search strategy (searched 28/02/16)

- 1 exp unsaturated fatty acid/
- 2 exp long chain fatty acid/
- 3 exp fish oil/
- 4 exp lipid/
- 5 (longchain polyunsaturated fatty acid* or long chain polyunsaturated fatty acid* or LCPUFA).tw.

- 6 (polyunsaturated fatty acid* or PUFA).tw.
- 7 (fish oil* or marine oil* or algal oil*).tw.
- 8 (docosahexaenoic acid* or DHA).tw.
- 9 arachidonic acid*.tw.
- 10 (icosapentaenoic acid* or eicosapentaenoic acid* or EPA).tw.
- 11 lipid*.tw.
- 12 (omega-3 or omega-6).tw.
- 13 (linoleic acid* or linolenic acid*).tw.
- 14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
- 15 exp prematurity/
- 16 exp low birth weight/
- 17 (small adj2 gestational age).tw.
- 18 ((low adj1 birthweight) or (low adj1 birth weight)).tw.
- 19 (preterm or pre-term or prematur* or lbw).tw.
- 20 17 or 18 or 19
- 21 (infan* or newborn* or neonate*).tw.
- 22 20 and 21
- 23 15 or 16 or 22
- 24 exp controlled clinical trial/
- 25 randomized controlled trial/
- 26 exp triple blind procedure/
- 27 single blind procedure/
- 28 double blind procedure/
- 29 crossover procedure/
- 30 clinical trial/
- 31 exp placebo/
- 32 exp randomization/
- 33 random*.tw.
- 34 placebo*.tw.
- 35 ((singl* or doubl* or trebl* or tripl*) adj1 (blind* or mask*)).tw.
- 36 (crossover or cross over).tw.
- 37 trial.tw.
- 38 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
- 39 (animal/ or non human/) not human/
- 40 38 not 39

41 14 and 23 and 40

Appendix 4. CINAHL (EBSCO) search strategy (searched 28/02/16)

S34 S12 AND S21 AND S33

S33 S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32

S32 (sing* OR doubl* OR tripl* OR trepl*) OR (blind* OR mask*)

S31 crossover OR cross over

S30 (MH "Crossover Design")

S29 trial

S28 random*

S27 (MH "Quantitative Studies")

S26 (MH "Random Assignment")S25 placebo*

S24 (MH "Placebos")

S23 PT clinical trial

S22 (MH "Clinical Trials+")

S21 S13 OR S14 OR S20

S20 S18 AND S19

S19 infan* OR newborn* OR neonate*

S18 S15 OR S16 OR S17

S17 preterm OR pre-term OR prematur* OR lbw

S16 low birthweight OR low birth weightS15 small for gestational age

S14 (MH "Infant, Low Birth Weight+")

S13 (MH "Infant, Premature")

S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11

S11 (linoleic acid* OR linolenic acid*)

S10 (omega-3 OR omega-6)

S9 lipid*

S8 (eicosapentaenoic acid* OR EPA)

S7 arachidonic acid*

S6 (docosahexaenoic acid* OR DHA)

S5 (fish oil* OR marine oil* OR algal oil*)

S4 (polyunsaturated fatty acid* OR PUFA)

S3 (longchain polyunsaturated fatty acid* OR long chain polyunsaturated fatty acid* OR LCPUFA)

S2 (MH "Lipids+")

S1 (MH "Fatty Acids, Unsaturated+")

Appendix 5. MEDLINE (OvidSP) In Process & Other Non-indexed Citations search strategy (search 28/02/16)

1 (longchain polyunsaturated fatty acid* or long chain polyunsaturated fatty acid* or LCPUFA).mp.

2 (polyunsaturated fatty acid* or PUFA).mp.

3 (fish oil* or marine oil* or algal oil*).mp.

4 (docosahexaenoic acid* or DHA).mp.

5 arachidonic acid*.mp.

6 (eicosapentaenoic acid* or EPA).mp.

7 lipid*.mp.

8 (omega-3 or omega-6).mp.

9 (linoleic acid* or linolenic acid*).mp.

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11 (small adj2 gestational age).mp.

12 ((low adj1 birthweight) or (low adj1 birth weight)).mp.

13 (preterm or pre-term or prematur* or lbw).mp.

14 11 or 12 or 13

15 (infan* or newborn* or neonate*).mp.

16 14 and 15

17 random*.mp.

18 placebo*.mp.

19 trial*.mp.

20 17 or 18 or 19

21 10 and 16 and 20

Appendix 6. 'Risk of bias' tool

We evaluated the following and entered the findings into the risk of bias tables:

1) Random sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorized the method used to generate the allocation sequence as:

- Low (any truly random process e.g. random number table; computer random number generator);
- High (any non random process e.g. odd or even date of birth; hospital or clinic record number);
- Unclear.

(2) Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorized the method used to conceal the allocation sequence as:

- Low (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- High (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- Unclear.

(3) Blinding (checking for possible performance bias and detection bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods as:

- Low, High or Unclear for participants;
- Low, High or Unclear for personnel;
- Low, High or Unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorized the methods as:

- Low (< 20% missing data);
- High ($\geq$ 20% missing data):
- Unclear.

(5) Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- Low (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- High (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- Unclear.

(6) Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- Low; High; or unclear.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
3 February 2017	Amended	External source of support added.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 1, 1999

Date	Event	Description
2 September 2016	New citation required but conclusions have not changed	Overall conclusions remain unchanged.
6 April 2016	New search has been performed	Literature search on 28 February 2016 did not identify any additional RCT for inclusion. 12 new 'excluded studies'. 10-year follow-up results of one previously included RCT have been added. 'Summary of findings' tables have been added. Two new authors.
28 December 2010	New citation required but conclusions have not changed	New first author.
10 December 2010	New search has been performed	<p>This updates the review "Longchain polyunsaturated fatty acid supplementation in preterm infants" published in the Cochrane Database of Systematic Reviews (Simmer 2000; Simmer 2004; Simmer 2008).</p> <p>Updated search in December 2009 identified two new trials for inclusion in this update (Carnielli 2007; Lapillonne 2000).</p> <p>No changes to the conclusions of the review.</p>
1 April 2010	New search has been performed	<p>This review updates the existing review of "Longchain polyunsaturated fatty acid supplementation in preterm infants" published in The Cochrane Library, Issue 1, 2008 (Simmer 2008).</p> <p>Two trials were added in this update. Results of the added trials confirmed that there are no significant benefits or risks of LCPUFA supplementation of formula for preterm infants.</p> <p>Growth was the only clinical outcome assessed in the two trials identified in this update. Both studies did not report benefits or harms related to LCPUFA supplementation in terms of growth at different time points in different populations.</p>
10 June 2008	Amended	Converted to new review format.
31 August 2007	New search has been performed	<p>This review updates the existing review of "Longchain polyunsaturated fatty acid supplementation in preterm infants" published in The Cochrane Library, Issue 1, 2004 (Simmer 2004).</p> <p>Five trials had been added in the previous update (Simmer 2004). Four trials were added in this update. Results of the added trials confirmed that there are no significant benefits or risks of LCPUFA supplementation of formula for preterm infants.</p> <p>Three out of four added trials reported some benefit for various developmental and growth outcomes at different time points in different populations.</p>

CONTRIBUTIONS OF AUTHORS

2000 original review:

KS: Design and preparation of protocol, literature search, assessment of eligibility and quality of studies, data extraction and data analysis, writing of manuscript.

2004 review update:

Longchain polyunsaturated fatty acid supplementation in preterm infants (Review)

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KS: Assessment of eligibility and quality of studies, review of manuscript.

SP: Literature search, assessment of eligibility and quality of studies, data extraction and data analysis, writing of manuscript.

2008 review update:

KS: Review of manuscript, guidance and supervision for planning of the meta-analysis.

SMS: Literature search, assessment of eligibility and quality of studies, data extraction and data analysis, writing of manuscript.

SP: Literature search, assessment of eligibility and study quality, review of manuscript.

2010 review update:

SMS: Literature search, assessment of eligibility and quality of studies, data extraction and data analysis, writing of manuscript.

SP: Assessment of eligibility and study quality, data extraction, review of manuscript.

KS: Assessment of eligibility and study quality, review of manuscript, guidance and supervision for update of the meta-analysis.

2016 review update:

SS: Review of the manuscript.

KS: Review of the manuscript.

SP: Review of the manuscript.

SR: Literature search, assessed eligibility and reassessed risk of bias of included studies, shared writing of manuscript.

KM: Literature search, assessed eligibility and reassessed risk of bias of included studies, added study flow diagram, bias graph and table, updated 'Summary of findings' table, shared writing of manuscript.

DECLARATIONS OF INTEREST

None.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Arachidonic Acid [administration & dosage]; Docosahexaenoic Acids [administration & dosage]; Fatty Acids, Unsaturated [*administration & dosage]; Infant Formula [*chemistry]; Infant Nutritional Physiological Phenomena; Infant, Premature [*growth & development]; Intelligence [physiology]; Randomized Controlled Trials as Topic; Vision, Ocular [physiology]; Visual Acuity [*physiology]

MeSH check words

Humans; Infant, Newborn