Article:
Walsh, Verena, Brown, Jennifer Valeska Elli, Askie, Lisa M et al. (2019) Nutrient-enriched formula versus standard formula for preterm infants. Cochrane Database of Systematic Reviews. CD004204. ISSN: 1469-493X

https://doi.org/10.1002/14651858.CD004204.pub3

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Nutrient-enriched formula versus standard formula for preterm infants (Review)

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Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD004204.
DOI: 10.1002/14651858.CD004204.pub3.

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[Intervention Review]

Nutrient-enriched formula versus standard formula for preterm infants

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 7, 2019.

Citation: Walsh V, Brown JVE, Askie LM, Embleton ND, McGuire W. Nutrient-enriched formula versus standard formula for preterm infants. *Cochrane Database of Systematic Reviews* 2019, Issue 7. Art. No.: CD004204. DOI: 10.1002/14651858.CD004204.pub3.

ABSTRACT

Background

Preterm infants may accumulate nutrient deficits leading to extrauterine growth restriction. Feeding preterm infants with nutrient-enriched rather than standard formula might increase nutrient accretion and growth rates and might improve neurodevelopmental outcomes.

Objectives

To compare the effects of feeding with nutrient-enriched formula versus standard formula on growth and development of preterm infants.

Search methods

We used the Cochrane Neonatal standard search strategy. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 11), MEDLINE, Embase, and the Cumulative Index to Nursing and Allied Health Literature (until November 2018), as well as conference proceedings, previous reviews, and clinical trials databases.

Selection criteria

Randomised and quasi-randomised controlled trials that compared feeding preterm infants with nutrient-enriched formula (protein and energy plus minerals, vitamins, or other nutrients) versus standard formula.

Data collection and analysis

We extracted data using the Cochrane Neonatal standard methods. Two review authors separately evaluated trial quality and extracted and synthesised data using risk ratios (RRs), risk differences, and mean differences (MDs). We assessed certainty of evidence at the outcome level using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.

Main results

We identified seven trials in which a total of 590 preterm infants participated. Most participants were clinically stable preterm infants of birth weight less than 1850 g. Few participants were extremely preterm, extremely low birth weight, or growth restricted at birth. Trials were conducted more than 30 years ago, were formula industry funded, and were small with methodological weaknesses (including lack of masking) that might bias effect estimates. Meta-analyses of in-hospital growth parameters were limited by statistical heterogeneity. There is no evidence of an effect on time to regain birth weight (MD -1.48 days, 95% confidence interval (CI) -4.73 to 1.77) and low-certainty evidence suggests that feeding with nutrient-enriched formula increases in-hospital rates of weight gain (MD 2.43 g/kg/d, 95% CI 1.60 to 3.26) and head circumference growth (MD 1.04 mm/week, 95% CI 0.18 to 1.89). Meta-analysis did not show an effect on the average rate of length gain (MD 0.22 mm/week, 95% CI -0.70 to 1.13). Fewer data are available for growth and developmental outcomes assessed beyond infancy, and these do not show consistent effects of nutrient-enriched formula feeding. Data from two trials did not show an effect on Bayley Mental Development Index scores at 18 months post term (MD 2.87, 95% CI -1.38 to 7.12; moderate-certainty evidence). Infants who received nutrient-enriched formula had higher Bayley Psychomotor Development Index scores at 18 months post term (MD 6.56. 95% CI 2.87 to 10.26; low-certainty evidence), but no evidence suggested an effect on cerebral palsy (typical RR 0.79, 95% CI 0.30 to 2.07; 2 studies, 377 infants). Available data did not indicate any other benefits or harms and provided low-certainty evidence about the effect of nutrient-enriched formula feeding on the risk of necrotising enterocolitis in preterm infants (typical RR 0.72, 95% CI 0.41 to 1.25; 3 studies, 489 infants).

Authors' conclusions

Available trial data show that feeding preterm infants nutrient-enriched (compared with standard) formulas has only modest effects on growth rates during their initial hospital admission. No evidence suggests effects on long-term growth or development. The GRADE assessment indicates that the certainty of this evidence is low, and that these findings should be interpreted and applied with caution. Further randomised trials would be needed to resolve this uncertainty.

PLAIN LANGUAGE SUMMARY

Nutrient-enriched formula for preterm infants

Review question

Does feeding preterm infants with nutrient-enriched formula (extra energy and protein) compared with standard formula increase the rate of growth and improve development?

Background

Standard formula (designed for term infants) may not provide preterm infants with sufficient quantities of nutrients to support optimal growth and development. Nutrient-enriched formula (containing extra protein and energy from carbohydrates or fat and other nutrients) has about 20% higher nutrient content than standard formula. Feeding preterm infants, particularly very preterm infants, with nutrient-enriched formula might increase nutrient intake and growth rates, and might improve development.

Study characteristics

We found seven trials; most were small (involving 590 infants in total), and some were prone to bias.

Key results

Nutrient-enriched versus standard formula for preterm infants does not reduce the time taken to regain birth weight but is associated with higher rates of weight gain and head growth (although not length gain) during neonatal unit stay after birth. Only limited data are available for growth and developmental outcomes assessed beyond infancy, and these do not show consistent effects. No evidence suggests other potential benefits or harms of nutrient-enriched formulas, including effects on feeding or bowel problems.

Conclusions

Although available trial data show that nutrient-enriched formulas increase growth rates of preterm infants during their initial hospital admission, they do not provide evidence of effects on longer-term growth or development. Further randomised trials would be needed to resolve this uncertainty.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Patient or population: preterm infants
Setting: healthcare setting
Intervention: nutrient-enriched formula
Comparison: standard formula

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard formula	Risk with nutrient-enriched formula			
Weight gain (g/kg/d)	Comparator	MD gain was 2.43 higher (1. 60 to 3.26 higher)	-	440 (6 RCTs)	⊕⊕◯◯ Low[a,b]
Length gain (mm/week)	Comparator	MD gain was 0.22 mm/week higher (0.7 lower to 1.13 higher)	-	386 (5 RCTs)	⊕⊕◯◯ Low[a,b]
Head circumference gain (mm/week)	Comparator	MD gain was 1.04 mm/week higher (0.18 to 1.89 higher)	-	399 (5 RCTs)	⊕⊕◯◯ Low[a,b]
Mental Development Index (MDI) at 18 months	Comparator	Mean MDI was 2.81 higher (1.44 lower to 7.06 higher)	-	310 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Psychomotor Development Index (PDI) at 18 months	Comparator	Mean PDI was 6.56 more (2. 87 to 10.26 more)	-	310 (2 RCT)	⊕⊕◯◯ Low[a,b]
Necrotising enterocolitis	Study population		RR 0.72 (0.41 to 1.25)	489 (3 RCTs)	⊕⊕◯◯ Low[a,c]
	112 per 1000	31 per 1000 (66 fewer to 28 more)			

*__The risk in the intervention group__ (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; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but may be substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

[a]Uncertainty about methods used to generate random sequence, conceal allocation, and mask assessments in trials.
[b]Moderate to high heterogeneity.
[c]Post hoc exclusions in two trials.

BACKGROUND

Description of the condition

Preterm infants (born before 37 weeks' gestation), especially very preterm infants (born before 32 weeks' gestation), have fewer nutrient reserves at birth than term infants and are subject to physiological and metabolic stresses that increase their nutrient needs. Recommended nutrient requirements for preterm infants based on intrauterine growth studies assume that the optimal rate of postnatal growth should be similar to that of uncompromised foetuses of an equivalent gestational age (Tsang 1993). However, these recommended levels of nutrient input and growth are rarely achieved. Most very preterm infants accumulate substantial energy, protein, mineral, and other nutrient deficits during their initial hospital stay (Embleton 2001; Horbar 2015). By the time they are ready to go home, typically at around 36 to 40 weeks' postmenstrual age, many infants are growth restricted relative to their term-born peers (Clark 2003; Dusick 2003). Growth deficits, which can persist through childhood and adolescence, are associated with neurodevelopmental impairment and with poor cognitive and educational outcomes (Bracewell 2008; Cooke 2003; Farooqi 2006; Ford 2000; Hack 1991; Leppänen 2014; Trebar 2007). Preterm infants who have accumulated mineral deficits have higher levels of metabolic bone disease and slower skeletal growth compared with infants born at term. Some uncertainty remains about long-term effects of such deficits on bone mass and health (Fewtrell 2011). Furthermore, there is concern that nutritional deficiency and growth restriction during early infancy may have consequences for long-term metabolic and cardiovascular health (Embleton 2013; Lapillonne 2013).

Description of the intervention

Human breast milk is the recommended form of enteral nutrition for preterm infants (AAP 2012). When sufficient human breast milk is not available, an artificial formula, given as the sole form of enteral nutrition or as a supplement to human breast milk, may be used as an alternative (Klingenberg 2012). A variety of formulas, typically adapted from cow's milk, are available. These vary in energy, protein, and mineral content and can be categorised broadly as follows.

- Standard ('term') formulas based on the composition of mature breast milk; the typical energy content is 67 to 70 kCal/100 mL, the concentration of protein is about 1.4 g to 1.7 g/100 mL, and the calcium and phosphate content is about 50 mg/100 mL and 30 mg/100 mL, respectively.
- Nutrient-enriched ('preterm') formulas, designed to provide nutrient intakes to match intrauterine accretion rates; these are energy enriched (typically to about 75 to 80 kCal/100 mL), protein enriched (2.0 to 2.4 g/100 mL) and variably enriched with minerals, vitamins, electrolytes, and trace elements (Hay 2017).

How the intervention might work

Feeding preterm infants formula enriched with energy, protein, minerals, and other nutrients may be expected to promote nutrient accretion and growth (increase in weight, length, and head circumference). High levels of nutrient intake during this critical period may be especially important for infants who are growth restricted or 'small for gestation' at birth, are unable to consume large quantities of milk, show slow postnatal growth, or have additional nutritional and metabolic requirements (Agostoni 2010; Klein 2002).

However, formula with high nutrient density might interfere with gastric emptying and intestinal peristalsis, or might perturb the microbiome, resulting in enteral feed intolerance or increased risk of necrotising enterocolitis (Embleton 2017; Hancock 1984; Ramani 2013; Shulhan 2017; Siegel 1984). Nutrient-enriched formula that is poorly tolerated may reduce intake and any putative benefit for growth and development. Furthermore, concern exists that rapid 'catch-up growth' with accelerated weight gain might be associated with altered fat distribution and related 'programmed' metabolic consequences that increase long-term risks of insulin resistance and cardiovascular disease (Doyle 2004; Euser 2005; Euser 2008).

Why it is important to do this review

Given that early enteral nutrition strategies may affect growth and development in preterm infants, and that uncertainty exists about the balance between possible benefits and harms, this Cochrane Review aimed to detect, appraise, and synthesise evidence from randomised controlled trials (RCTs) to inform policy, practice, and research.

This review focuses on the effects of feeding preterm infants with nutrient-enriched formula versus standard formula during initial hospitalisation after birth. Related Cochrane Reviews have assessed the effects of feeding preterm infants nutrient-enriched formula versus standard formula after hospital discharge (Young 2016), and of providing multi-nutrient fortification of human milk for feeding preterm infants (Brown 2016).

OBJECTIVES

To compare the effects of feeding with nutrient-enriched formula versus standard formula on growth and development of preterm infants.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs or quasi-RCTs. Quasi-RCTs are trials that do not use a true method of randomisation and that allocate participants to the arms of the trial based on date of birth, hospital number, or another non-random method.

Types of participants

Preterm infants (less than 37 weeks' gestation at birth) fed formula (exclusively or as a supplement to human breast milk) during birth hospitalisation.

Types of interventions

- Nutrient-enriched formula: both energy content > 72 kcal/100 mL and protein content > 1.7 g/100 mL

versus

- Standard formula: both energy content ≤ 72 kcal/100 mL and protein content ≤ 1.7 g/100 mL

The formula could be fed as the sole diet or as a supplement to human breast milk. Infants in trial groups should have received similar care but not similar types of formula. The intervention should have been intended to continue for at least two weeks to allow measurable effects on growth.

Types of outcome measures

Primary outcomes

Growth

- Time to regain birth weight and subsequent rates of weight gain, linear growth, head growth, or skinfold thickness growth up to six months post term
- Long-term growth: weight, height, or head circumference (or proportion of infants who remain below the 10th percentile for index population distribution, or both) assessed at intervals from six months post term

Neurodevelopment

- Death or severe neurodevelopmental disability defined as any one or a combination of the following: non-ambulant cerebral palsy, developmental quotient more than two standard deviations below the population mean, and blindness (visual acuity < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification)
- Neurodevelopmental scores in children aged at least 12 months, measured via validated assessment tools such as Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III), main domains (cognitive, motor, language)
- Cognitive and educational outcomes in children five years of age or older.

Necrotising enterocolitis

Necrotising enterocolitis confirmed at surgery or at autopsy or diagnosed by at least two of the following clinical features (Kliegman 1987).

- Abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen.
- Abdominal distension with abdominal radiograph showing gaseous distension or frothy appearance of bowel lumen (or both).
- Blood in stool.
- Lethargy, hypotonia, or apnoea (or a combination of these).

Secondary outcomes

- Duration of birth hospitalisation (days)
- Feed intolerance during the trial intervention period that results in cessation of enteral feeding for longer than four hours
- All-cause mortality before hospital discharge
- Measures of body composition (lean/fat mass) and growth parameters including z-score for weight, length, and head circumference, skinfold thickness, body mass index, and proportion of infants who remain below the 10th percentile for the index population distribution of weight, length, or head circumference at 44 weeks' postmenstrual age and beyond
- Measures of bone mineralization, such as serum alkaline phosphatase level, or bone mineral content assessed by dual energy X-ray absorptiometry (DEXA) at 44 weeks' postmenstrual age and beyond
- Measures of long-term metabolic or cardiovascular health, including insulin resistance, obesity, diabetes, and hypertension

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal.

Electronic searches

The search strategy was developed in Ovid MEDLINE and consisted of terms for preterm or low birthweight infants combined with terms for formula milk. The search was limited to RCTs using the sensitivity maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011). We applied no language or date limits. The MEDLINE search strategy was translated for use in the other databases searched (Appendix 1).

We searched the following databases.

- MEDLINE (Ovid SP, 1946 to 9 November 2018).
- Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library; 2018, Issue 11).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus) (EBSCO, 1982 to 12 November 2018).
- Embase (Ovid SP, 1974 to 9 November 2018).
- Maternity and Infant Care (Ovid SP, 1971 to 30 September 2018).
- PubMed (1966 to 12 November 2018).

In addition, we searched ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/) on 16 November 2018 to identify ongoing and completed trials.

Searching other resources

We examined the references provided in studies identified as potentially relevant. We searched the reference lists of any articles selected for inclusion in this review to identify additional relevant articles. We searched the abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2019), the European Society for Paediatric Research (1995 to 2019), the UK Royal College of Paediatrics and Child Health (2000 to 2019), and the Perinatal Society of Australia and New Zealand (2000 to 2019). We considered trials reported only as abstracts to be eligible if sufficient information was available from the trial report, or from contact with study authors, to fulfil the inclusion criteria.

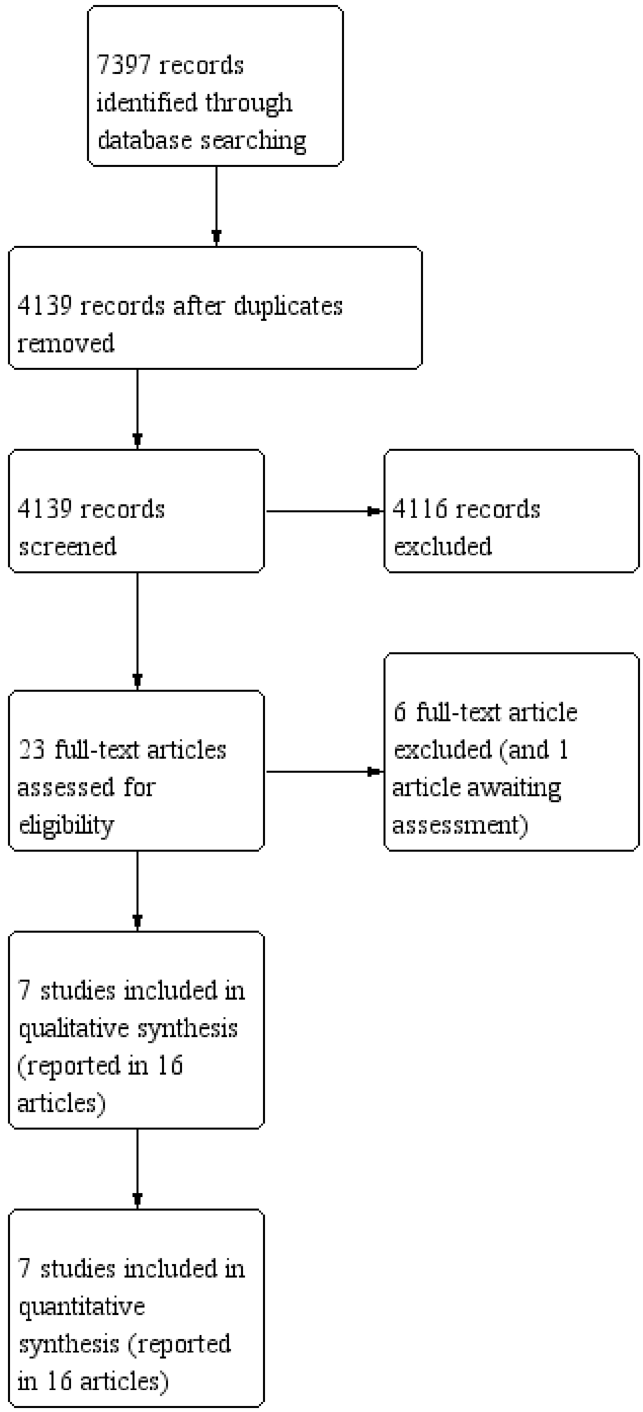
Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

We screened the title and abstract of all studies identified by the above search strategy, and two review authors (VW and JB) independently assessed the full articles for all potentially relevant trials. We discussed any disagreements until consensus was achieved. We excluded studies that did not meet the inclusion criteria and listed all studies excluded after full-text assessment and reasons for their exclusion in the Characteristics of excluded studies table. The study selection process is illustrated in a PRISMA diagram (Figure 1), and study selection was managed using Rayyan (Ouzzani 2016).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (VW and JB, or VW and WM) used Covidence to independently extract from each included study information on design, methods, participants, interventions, outcomes, and treatment effects(Veritas Health Innovation). We discussed any disagreements until we reached a consensus.

Assessment of risk of bias in included studies

Two review authors (VW and JB) used Covidence to independently assess risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2017).

- 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.

We resolved disagreements by discussion or by consultation with a third review author (WM or NDE). We did not exclude trials on the basis of risk of bias. See Appendix 2 for a description of each domain.

Measures of treatment effect

We analysed treatment effects in individual trials and reported risk ratio (RR) and risk difference (RD) values for dichotomous data and mean difference (MD) values for continuous data, along with respective 95% confidence intervals (CIs). We planned to determine the number needed to treat for an additional beneficial outcome or the number needed to treat for an additional harmful outcome for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant.

Dealing with missing data

Due to the age of the included studies (all published before 2000), we did not contact any original study investigators. We imputed missing standard deviations (SDs) using reported sample sizes and standard error values.

Assessment of heterogeneity

Two review authors (NDE and WM) assessed clinical heterogeneity, and we conducted meta-analyses when both review authors agreed that study participants, interventions, and outcomes were similar.

We examined treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. When we detected high levels of heterogeneity ($I^2 > 75\%$), we explored possible sources (e.g. differences in study design, participants, or interventions; completeness of outcome assessments).

Assessment of reporting biases

We planned to inspect funnel plots for asymmetry if data from ten or more trials were included in a meta-analysis.

Data synthesis

We used a fixed-effect model for meta-analyses.

Summary of findings and certainty of evidence

We assessed the certainty of the body of evidence for the main comparisons at the outcome level using the GRADE approach (Schünemann 2013; see Appendix 3). Two review authors (JB and WM) independently assessed the certainty of the evidence for outcomes identified as critical or important for clinical decision-making: growth, development, and necrotising enterocolitis.

We considered trial evidence as high certainty but downgraded this by one level for serious (or by two levels for very serious) limitations based upon design (risk of bias), consistency across studies, directness, precision of estimates, and presence of publication bias. We used the GRADEpro Guideline Development Tool (GDT) to create a 'Summary of findings' table to report the certainty of the evidence (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

When data were available, we planned subgroup analyses of:

- trials in which infants received formula only versus those where formula could be given as a supplement to breast milk;
- extremely preterm (< 28 weeks' gestation) infants versus infants born at 29 to 36 weeks' gestation; and
- infants with birth weight below the 10th percentile for the reference population ('small for gestation') versus infants with

birth weight at or above the 10th percentile ('appropriate for gestation').

Sensitivity analysis

We planned sensitivity analyses to determine whether our findings are affected by including only studies reporting adequate methods (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

RESULTS

Description of studies

Results of the search

See Figure 1.

We included seven trials (Kashyap 1986; Kulkarni 1984; Lucas 1989a; Lucas 1989b; Siripoonya 1989; Thom 1984; Yesilipek 1992).

One trial report is awaiting assessment (Costa 1996).

We did not identify any ongoing trials.

We excluded six full-text reports (Atkinson 1981; Duman 2000; Haque 1987; Hering 1987; Pridham 1999; Yin 2004).

Included studies

Included trials were undertaken during the 1970s and 1980s by investigators in neonatal units in the UK, the USA, Turkey, Thailand, and South Africa (see Characteristics of included studies). Five of these trials were conducted at single centres (Kashyap 1986; Kulkarni 1984; Siripoonya 1989; Thom 1984; Yesilipek 1992). Two trials were conducted across two centres (Lucas 1989a; Lucas 1989b).

Participants

In total, 590 infants participated in the included trials (range, 22 to 264). Of these, 444 infants (> 75%) participated in the two largest trials (Lucas 1989a; Lucas 1989b). Most participants were clinically stable preterm infants of birth weight less than 1850 g. Few participants were extremely preterm, extremely low birth weight, or growth restricted. The trials, in general, excluded from participation infants with congenital anomalies and those with respiratory, gastrointestinal, or neurological problems.

Interventions

Six trials assessed the use of nutrient-enriched versus standard formula as the sole diet; one assessed formula use supplemental to human milk (Lucas 1989b). Formulas were typically commenced when infants were assessed as being clinically stable and able to tolerate enteral feeds. Trial participants continued to receive the intervention or control formula for several weeks or until they reached a specified weight (typically about 2 kg). Most trials stipulated a target volume of milk intake for both groups (typically 150 to 180 mL/kg/d).

Outcomes

Most of the trials aimed to assess effects of the intervention on growth rates during birth hospitalisation (time to regain birth weight and rate of gain in weight, length, or head circumference while in hospital or until reaching a specified weight). One trial's primary objective was to assess effects on bone mineralization (Kulkarni 1984). Two trials reported neurodevelopmental or long-term growth outcomes (Lucas 1989a; Lucas 1989b). These trials measured participants' blood pressure and assessed insulin resistance in a subset (< 20%) of the trial cohort aged 13 to 16 years.

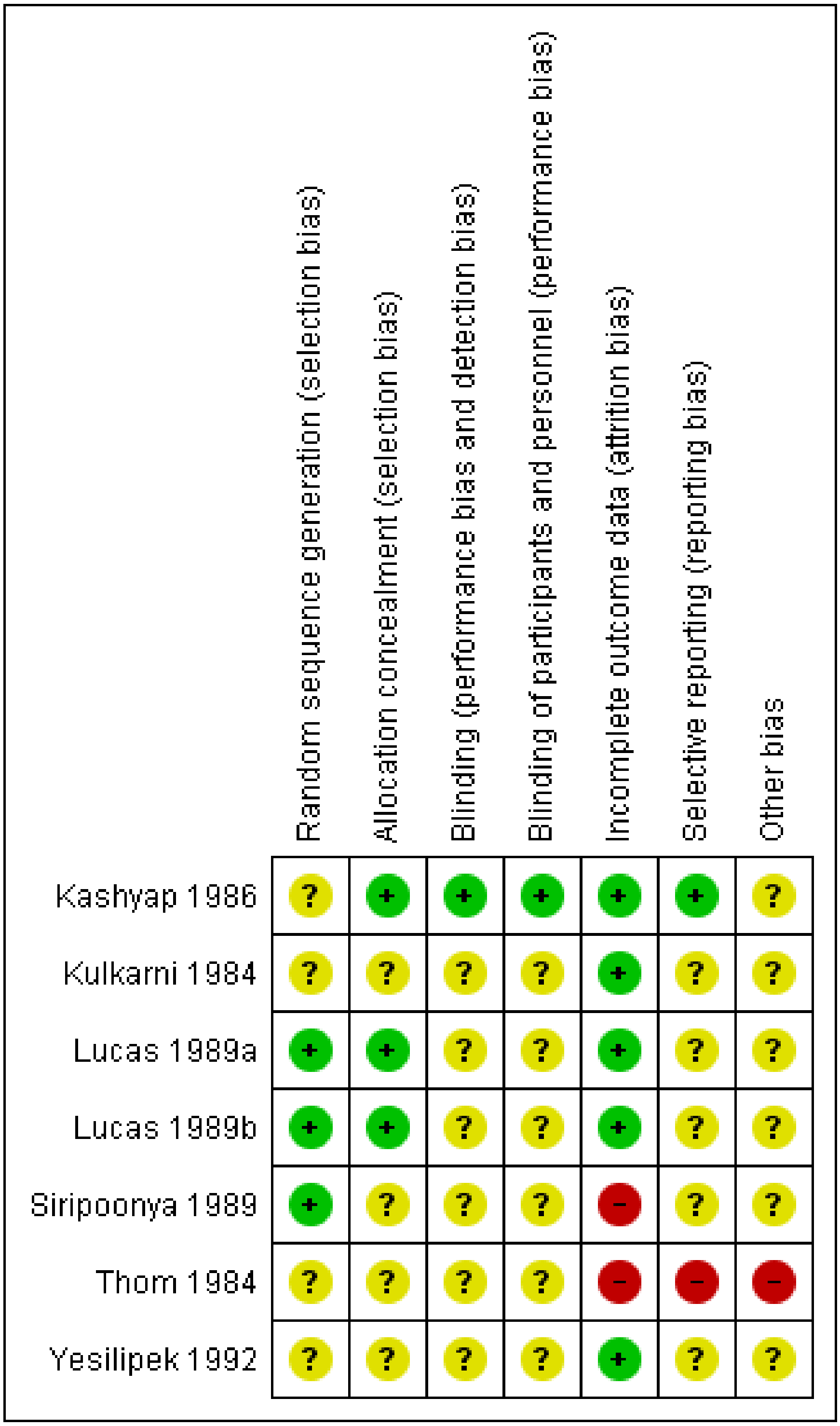
Excluded studies

We excluded five studies following review of the full text of the report (Atkinson 1981; Duman 2000; Haque 1987; Hering 1987; Pridham 1999; see Characteristics of excluded studies).

Risk of bias in included studies

Quality assessments are detailed in the Characteristics of included studies table and are illustrated in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Overall, we found risk of bias difficult to assess because reporting was limited. Consequently, we scored most items as having unclear risk.

Allocation

Two trial reports described methods used to ensure adequate sequence generation (random numbers table) and allocation concealment (sealed, numbered envelopes); we assessed these trials as being at low risk of bias (Lucas 1989a; Lucas 1989b). The other trials did not report methods of sequence generation or allocation concealment used (unclear risk of bias)

Blinding

One trial report described masking of study personnel and parents or caregivers to formula types; we assessed this trial as being at low risk of bias (Kashyap 1986). The other trial reports did not state whether investigators or staff were masked (unclear risk of bias). In the two trials that assessed longer-term (post infancy) growth and neurodevelopmental outcomes, assessors were unaware of the intervention group to which infants belonged (Lucas 1989a; Lucas 1989b).

Incomplete outcome data

Most trials reported complete follow-up for the in-hospital outcomes assessment; we assessed them as being at low risk of attrition bias. In three trials, infants who developed complications (5% to 10% of the total enrolled) were withdrawn from the study; therefore in-hospital growth data for these infants were not presented. In the two trials that reported data for long-term outcomes, more than 80% of participants were assessed for growth and neurodevelopmental parameters (Lucas 1989a; Lucas 1989b). These trials assessed measures of cardiovascular and metabolic health in a subset (< 20%) of study participants aged 13 to 16 years. It is unclear whether or how participants were selected to undergo these assessments.

Selective reporting

We were unable to assess reliably whether selective reporting occurred as we did not have protocols or other indicators of prespecified outcomes for any of the included trials.

Other potential sources of bias

The manufacturer of the formula being tested funded six trials (Kashyap 1986; Kulkarni 1984; Lucas 1989a; Lucas 1989b; Siripoonya 1989; Thom 1984). One trial did not report the source of funding (Yesilipek 1992).

Effects of interventions

See: **Summary of findings for the main comparison** Nutrient-enriched formula for preterm infants

Primary outcomes

1. Days to regain birth weight (Outcome 1.1)

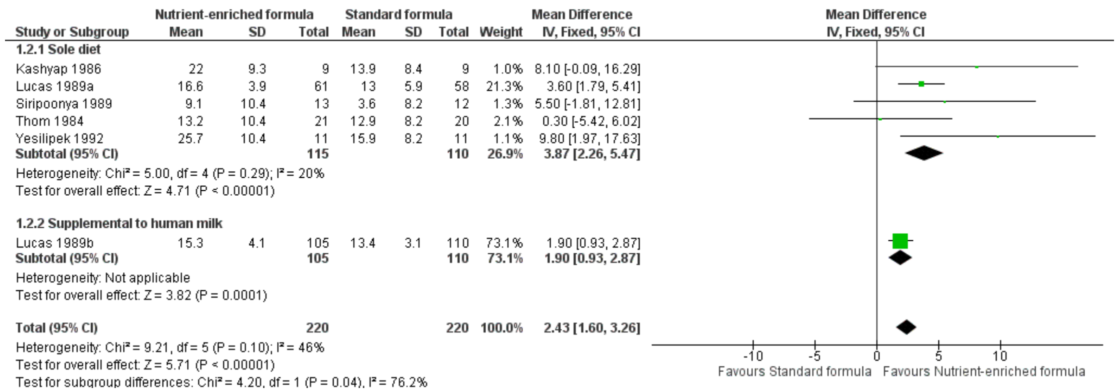
Three trials reported data (Kashyap 1986; Kulkarni 1984; Siripoonya 1989). Meta-analysis did not show an effect: MD 1.48, 95% CI -4.73 to 1.77; I^2 = 57% (Analysis 1.1).

2. Rate of weight gain (Outcome 1.2)

Six trials reported data (Kashyap 1986; Lucas 1989a; Lucas 1989b; Siripoonya 1989; Thom 1984; Yesilipek 1992). Two of these trials did not report SD values (Siripoonya 1989; Thom 1984). We imputed these from the trials with the nearest sample size (Higgins 2017).

Meta-analysis showed that weight gain was faster among infants fed nutrient-enriched formula: MD 2.43 g/kg/d, 95% CI 1.60 to 3.26; I^2 = 46% (Analysis 1.2; Figure 3).

Figure 3. Forest plot of comparison: 1 Nutrient-enriched formula vs standard formula, outcome: 1.2 Rate of weight gain (g/kg/d).



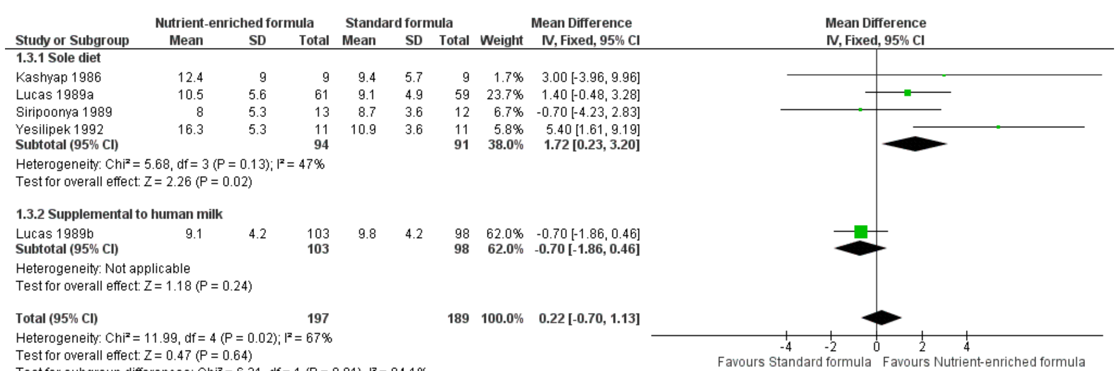
Kulkarni 1984 did not report numerical data but stated that there was no difference in the average daily rate of weight gain.

3. Rate of length gain (Outcome 1.3)

Five trials reported numerical data (Kashyap 1986; Lucas 1989a; Lucas 1989b. Siripoonya 1989; Yesilipek 1992). Siripoonya 1989 did not report SD values, so we imputed these from the trial with the nearest sample size.

Meta-analysis did not show a statistically significant effect: MD 0.22 mm/week, 95% CI -0.70 to 1.13; I^2 = 67% (Analysis 1.3; Figure 4).

Figure 4. Forest plot of comparison: 1 Nutrient-enriched formula vs standard formula, outcome: 1.3 Rate of length gain (mm/week).



Thom 1984 did not report numerical data but stated that there was no difference in the average daily rate of length gain.

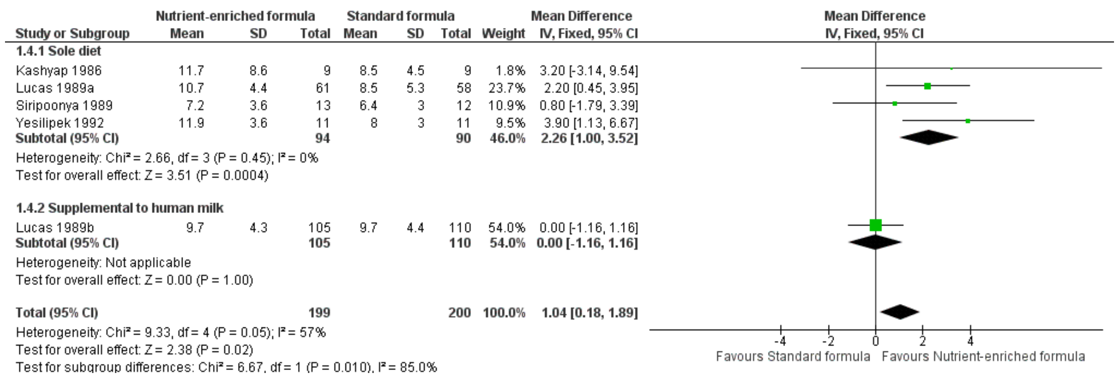
Three trials did not report rate of length gain (Kulkarni 1984; Lucas 1989a; Lucas 1989b).

4. Rate of head circumference gain (Outcome 1.4)

Five trials reported data (Kashyap 1986; Lucas 1989a; Lucas

1989b; Siripoonya 1989; Yesilipek 1992). Siripoonya 1989 did not report SD values. We imputed these from Yesilipek 1992, the trial with the nearest sample size.
Meta-analysis showed that head circumference growth was faster among infants fed nutrient-enriched formula: MD 1.04 mm/week, 95% CI 0.18 to 1.89; I² = 57% (Analysis 1.4; Figure 5).

Figure 5. Forest plot of comparison: 1 Nutrient-enriched formula vs standard formula, outcome: 1.4 Rate of head circumference gain (mm/week).



Two trials did not report rate of head circumference gain (Kulkarni 1984; Thom 1984).

5. Rate of skinfold thickness gain (Outcome 1.5 to 1.6)

Four trials reported numerical data for triceps skinfold thickness gain (Kashyap 1986; Lucas 1989a; Lucas 1989b; Siripoonya 1989). Siripoonya 1989 did not report SD values. We imputed these from Kashyap 1986. Three trials reported data for subscapular skinfold thickness gain (Kashyap 1986; Lucas 1989a; Lucas 1989b).
Infants in the nutrient-enriched formula group had statistically significant higher rates of:

- triceps skinfold thickness gain: MD 0.12 mm/week, 95% CI 0.07 to 0.17 (Analysis 1.5); and
- subscapular skinfold thickness gain: MD 0.10 mm/week, 95% CI 0.04 to 0.16 (Analysis 1.6).

6. Long-term growth (Outcome 1.7 to 1.16)

Two trials reported growth parameters beyond six months post term (Lucas 1989a; Lucas 1989b).
Meta-analyses showed no statistically significant differences in average:

- weight at 18 months (MD 0.06 kg, 95% CI -0.21 to 0.33; Analysis 1.7) or at 7.5 to 8 years post term (MD 0.30 kg, 95% CI -0.55 to 1.15; Analysis 1.8);
- height at 18 months (MD 0.31 cm, 95% CI -0.43 to 1.06; Analysis 1.9) or 7.5 to 8 years post term (MD 0.93 cm, 95% CI -0.30 to 2.16; Analysis 1.10);
- head circumference at 18 months (MD 0.09 cm, 95% CI -0.26 to 0.43; Analysis 1.11) or 7.5 to 8 years post term (MD -0.12 cm, 95% CI -0.45 to 0.21; Analysis 1.12);
- triceps skinfold thickness at 18 months (MD 0.01 mm, 95% CI -0.42 to 0.45; Analysis 1.13) or 7.5 to 8 years post term (MD -0.16 mm, 95% CI -0.91 to 0.60; Analysis 1.14); or
- subscapular skinfold thickness at 18 months (MD -0.14 mm, 95% CI -0.40 to 0.13; Analysis 1.15) or 7.5 to 8 years post term (MD -0.05 mm, 95% CI -0.67 to 0.57; Analysis 1.16).

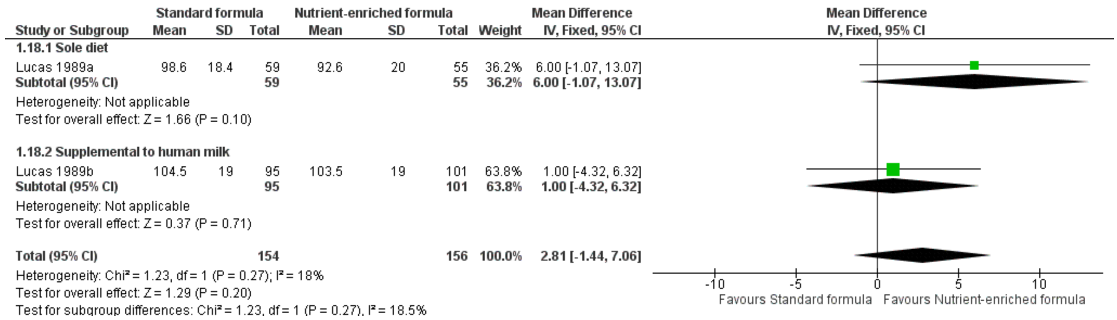
7. Neurodevelopmental outcomes (Outcome 1.17 to 1.18)

Two trials reported the number of infants with a diagnosis of cerebral palsy when assessed at age 18 months post term follow-up assessment (Lucas 1989a; Lucas 1989b). Meta-analysis did not show a statistically significant difference: typical RR 0.79, 95% CI 0.30 to 2.07; I² = 0% (Analysis 1.17).
None of the trials reported blindness or deafness as an outcome.

Two trials reported neurodevelopmental outcomes assessed via validated tools (Lucas 1989a; Lucas 1989b). Meta-analyses did not show a difference in:

- Bayley Mental Development Index (MDI) scores at 18 months post term: MD 2.87, 95% CI -1.38 to 7.12; I^2 = 15% (Analysis 1.18; Figure 6); or

Figure 6. Forest plot of comparison: 1 Nutrient-enriched formula vs standard formula, outcome: 1.18 Bayley (1) Mental Development Index at 18 months post term.



- Wechsler Revised Intelligence Scale for Children verbal, performance, and overall scores at 7.5 to 8 years post term (Analysis 1.19).

Meta-analysis showed a statistically significantly higher score in the nutrient-enriched formula-fed group for:

- Bayley Psychomotor Development Index (PDI) at 18 months post term: MD 6.56, 95% CI 2.87 to 10.26; I^2 = 91% (Analysis 1.18; Figure 6).

8. Necrotising enterocolitis (Outcome 1.22)

Three trials reported data (Lucas 1989a; Lucas 1989b; Thom 1984).
Meta-analysis did not show a statistically significant effect: typical RR 0.72, 95% CI 0.41 to 1.25; I^2 = 18%; RD -0.01, 95% CI -0.06 to 0.04 (Analysis 1.23).

Secondary outcomes

9. Duration of birth hospitalisation (Outcome 1.23)

One trial reported numerical data (Kulkarni 1984). There was no statistically significant difference in duration of hospitalisation (Analysis 1.24).

11. Feed intolerance

This outcome was not reported by any of the trials.

12. All-cause mortality (Outcome 1.24)

Two trials reported all-cause mortality (Lucas 1989a; Lucas 1989b). These trials reported mortality until 18 months post term. Because it is likely that most mortality in this population occurred before hospital discharge, we made a consensus decision to include the data.
Neither trial nor a meta-analysis showed a statistically significant difference: typical RR 1.12, 95% CI 0.65 to 1.93; I^2 = 0%; RD 0.01, 95% CI -0.05 to 0.07 (Analysis 1.25).

13. Measures of body composition (Outcome 1.25 to 1.27)

Two trials reported body mass index on long-term follow-up (Lucas 1989a; Lucas 1989b). Neither trial nor a meta-analysis showed a statistically significant difference at:

- 18 months post term (Analysis 1.26); nor
- 7.5 to 8 years (Analysis 1.27).

Two trials reported the waist-to-hip ratio at 7.5 to 8 years. Neither trial nor a meta-analysis showed a statistically significant difference (Analysis 1.28).

14. Measures of bone mineralization (Outcome 1.29 to 1.30)

Two trials reported serum alkaline phosphatase levels after four weeks of the trial intervention (Kashyap 1986; Kulkarni 1984). Meta-analysis did not show a statistically significant difference (Analysis 1.29).

One trial reported bone mineral content assessed by DEXA at 8 to 12 years (Lucas 1989a). Analyses did not show any statistically significant differences in lumbar spine, femoral neck, radius, or whole body bone mineral content (Analysis 1.30).

15. Measures of long-term metabolic or cardiovascular health

Two trials reported mean diastolic and systolic arterial blood pressure at ages 13 to 16 years for a subset (about 20% of surviving infants) of the trial cohort (Lucas 1989a; Lucas 1989b). The report stated that there were no statistically significant differences between groups but did not provide trial-specific data for meta-analyses.

Two trials reported plasma glucose, insulin, and proinsulin levels at ages 13 to 16 years for a subset (about 20%) of the trial cohort (Lucas 1989a; Lucas 1989b). The report stated that there were no statistically significant differences between groups but did not provide trial-specific data for meta-analyses.

Subgroup analyses

Nutrient-enriched or standard formula as sole diet or supplemental to human milk

Six trials compared feeding with formula as a sole diet (Kashyap 1986; Kulkarni 1984; Lucas 1989a; Siripoonya 1989; Thom 1984; Yesilipek 1992). One trial compared feeding with formula as a supplement to breast milk (Lucas 1989b). Analyses showed significant subgroup effects in favour of sole diet for:

- rate of head circumference gain (mm/week): test for subgroup differences: $Chi^2 = 4.22$, df = 1 (P = 0.04), $I^2 = 76.3\%$ (Analysis 1.4); and
- Bayley Psychomotor Development Index at 18 months: test for subgroup differences: $Chi^2 = 11.59$, df = 1 (P = 0.0007), $I^2 = 91.4\%$ (Analysis 1.20).

Extremely preterm (< 28 weeks' gestation) infants versus infants born at 29 to 36 weeks' gestation

Subgroup data were not available.

Infants with birth weight < 10th percentile for reference population versus infants with birth weight ≥ 10th percentile

Subgroup data were not available.

Sensitivity analysis

We were unable to undertake planned sensitivity analyses to determine whether findings are affected by including only studies using adequate methods (low risk of bias) as no trial fulfilled the prespecified criteria (adequate randomisation and allocation concealment, blinding of intervention and measurement, and < 10% loss to follow-up).

DISCUSSION

Summary of main results

We included seven RCTs in which a total of 590 preterm infants participated. Meta-analyses show that infants who receive nutrient-enriched formula have higher in-hospital rates of weight gain and head growth (although not in gain in length) than infants who receive standard formula. The effect on rate of weight gain is similar in trials that supplied formula as a sole diet and in the trial that supplied formula supplemental to human milk. A prespecified subgroup analysis shows that the effect on rate of head circumference growth was greater in trials that provided formula as the sole diet than in the trial of supplemental formula use. Follow-up of infants who participated in two of the largest trials did not show any effects on long-term growth nor on neurodevelopmental outcomes, with the exception of a significantly higher score for the Bayley Psychomotor Development Index (PDI) in one trial (Lucas 1989a).

Overall completeness and applicability of evidence

These findings should be interpreted and applied with caution. All trials were conducted more than 30 years ago. Most participants were stable preterm infants of low birth weight, but a few were extremely preterm or of extremely low birth weight, limiting the applicability of findings to the population at highest risk of postnatal growth restriction secondary to suboptimal nutrient intake. Although meta-analysis shows that nutrient-enriched formula increases the in-hospital rate of weight gain, the effect size is modest. The average daily rate of weight gain is about 2.5 g/kg higher among infants fed nutrient-enriched versus standard formula (about 75 g per month for a 1-kg infant).

Meta-analyses of growth outcomes showed moderate to high levels of statistical heterogeneity that were not explained by major differences in trial design or conduct. Participants in these trials were similar (most were stable preterm infants). Although different trials used a range of commercially prepared "preterm" formulas, these contained similar levels of energy (about 80 kcal/100 mL) and protein (> 2.0 g/100 mL) plus proportionate supplements of minerals, vitamins, and trace elements. These levels of energy and protein, however, are towards the lower bounds of current recommended intakes needed to match intrauterine accretion (based on receiving about 150 mL/kg/d of milk), and this is a possible explanation for the modest effect of the intervention on in-hospital growth parameters. These findings are consistent with those of another Cochrane Review, which showed that human milk-fed preterm infants who received milk fortified with extra energy and protein (to similar total levels as nutrient-enriched formula) gained weight at about 1.8 g/kg/d faster than infants who received unfortified breast milk (Brown 2016).

As well as uncertainty about the importance of these effects on in-hospital growth rates, uncertainty remains about their long-term impact on growth and development. The two trials that reported data on outcomes beyond infancy did not show differences in any growth parameters when assessed at 18 months and at 7.5 to 8 years. Similarly, neurodevelopmental assessments, which were completed in more than 80% of trial participants at 18 months, did not show evidence of effects on cognitive outcomes. Infants who received nutrient-enriched formula as a sole diet, however, had higher scores for psychomotor outcomes assessed at 18 months (Lucas 1989a). The importance of this finding is uncertain given that the predictive value of the Bayley Scales for later development of very preterm infants is low, with the Bayley Psychomotor Scale explaining 12% of later motor functioning (Luttikhuizen 2013).

Meta-analysis did not indicate that feeding with nutrient-enriched formula has important effects on the risk of necrotising enterocolitis. However, the risk of developing necrotising enterocolitis was reported in only three of the seven trials, and the upper bound of the 95% confidence interval (CI) does not exclude an increase in risk up to 25% (Lucas 1989a; Lucas 1989b; Thom 1984). In two trials, infants who developed necrotising enterocolitis were excluded from ongoing participation (post randomisation) but group-specific data were not available (Kashyap 1986; Kulkarni 1984).

A final major limitation of this review is that most included trials were undertaken at healthcare facilities in high-income countries, and none were conducted in community settings or in low-income countries. Reported evidence therefore may be of limited use to inform care practice in the resource-limited settings where most preterm and low birth weight infants are cared for globally (Imdad 2013).

Quality of the evidence

Using GRADE methods, we assessed the quality of the evidence as low or moderate for the prespecified outcomes (Summary of findings for the main comparison). The trials exhibited various weaknesses in methodological quality, specifically regarding allocation concealment methods and lack of masking in most. Parents, caregivers, clinicians, and investigators were likely to have been aware of the treatment group to which infants had been allocated, and this knowledge may have affected some care practices or investigation strategies, including thresholds for other interventions and investigations. Most meta-analyses showed evidence of moderate to high heterogeneity, and pooled estimates of effect had wide 95% CIs.

Potential biases in the review process

It is possible that our findings were subject to publication and other reporting biases, including greater availability of numerical data for inclusion in meta-analyses from trials that reported statistically significant or clinically important effects. This is important given that six of the included trials were funded or supported by manufacturers of the formulas being assessed (one trial did not report the source of funding or support). Some concern exists that formula manufacturers may selectively promote study findings from trials of specialist formulas as part of a marketing strategy that subverts UNICEF Baby Friendly Initiative regulations (Cleminson 2015; WHO 2018).

We attempted to minimise the threat of publication bias by screening the reference lists of included trials and related reviews and by searching the proceedings of the major international perinatal conferences to identify trial reports that are not yet published in full form in academic journals. However, we cannot be sure whether other trials have been undertaken but not reported, and concern remains that such trials are less likely than published trials to have detected statistically significant or clinically important effects. The meta-analyses that we performed did not include sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides low-certainty evidence that feeding preterm infants with nutrient-enriched formula compared with standard formula is associated with modest short-term increases in weight gain and head growth. These short-term gains in growth do not appear to lead to important long-term effects on growth or development. We did not show an increase in the risk of adverse outcomes including necrotising enterocolitis among infants who received nutrient-enriched formula, although the total number of infants studied was small and the data that could be abstracted from published studies were few.

Implications for research

Given the potential for nutrient-enriched formula feeding to affect important outcomes in preterm infants, this intervention merits further assessment. As this practice is already widely established and accepted in many neonatal units (particularly in high-income countries), it is important for researchers to determine whether families and clinicians would support a trial of this intervention. Trials should be powered to detect important effects on growth rates, as well as potential adverse consequences, during infancy and beyond. Trials should attempt to ensure that caregivers and assessors are masked to the intervention. Although this goal is more easily achievable for longer-term assessments, it is also important for ascertainment of adverse events, such as feeding intolerance and necrotising enterocolitis, when the threshold for investigation or diagnosis may be affected by knowledge of the intervention.

ACKNOWLEDGEMENTS

We thank Melissa Harden, Information Specialist, for developing the electronic search strategy.

The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kashyap 1986

Methods	Randomised controlled trial
Participants	Preterm infants of birth weight 900 to 1750 g (excluding infants with gastrointestinal tract, renal, or respiratory problems)
Interventions	**Sole diet:** Nutrient-enriched formula (N = 11) • *Energy (kcal/100 mL)*: 82.4 • *Protein (g/100 mL)*: 1.98 • *Target intake (mL/kg/d)*: 180 Standard formula (N = 12) • *Energy (kcal/100 mL)*: 62.5 • *Protein (g/100 mL)*: 1.26 • *Target intake (mL/kg/d)*: 180
Outcomes	Time to regain birth weight Rate of weight, length, and head circumference gain Rate of skinfold thickness gain - triceps and subscapular
Identification	**Sponsorship source:** US National Institute of Health Research grants (HD13020, AM27358, RR00645); Bristol-Myers Grant **Setting:** Department of Pediatrics, Columbia University College of Physicians & Surgeons, USA (early 1980s)
Notes	Infants were randomised into 3 groups. Only data from group 1 ("standard formula") and group 3 ("nutrient-enriched formula") were included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...assigned randomly shortly after birth to receive one of three formulas" - sequence generation not described
Allocation concealment (selection bias)	Low risk	Allocated colour-coded formula - investigators and nurses did not know how the codes applied to the formulas
Blinding (performance bias and detection bias) All outcomes	Low risk	Not described

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Formula containers were colour coded, with code known to neither the investigator nor nurses caring for the infants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome assessments likely to include complete cohort
Selective reporting (reporting bias)	Low risk	A trial protocol could not be found, but data for all outcomes described in the methods section of the paper were reported in the results
Other bias	Unclear risk	The study was funded by a pharmaceutical company. It is unclear if this company was also the manufacturer of the formulas used in the study Infants in the standard formula group had slightly higher mean birth weight

Kulkarni 1984

Methods	Randomised controlled trial
Participants	Preterm infants of birth weight < 1501 g (excluding infants with "severe malformations, or prolonged ventilatory assistance"). Infants were excluded *post randomisation* if they failed to achieve enteral intake of 80 kcal/kg/d by 5 weeks of age and/or if they developed necrotising enterocolitis (unclear if this was planned)
Interventions	**Sole diet:** Nutrient-enriched formula (N = 13) • *Energy (kcal/100 mL)*: 81 • *Protein (g/100 mL)*: 2.2 • *Target intake (mL/kg/d)*: not stated Standard formula (N = 18) • *Energy (kcal/100 mL)*: 68 • *Protein (g/100 mL)*: 1.55 • *Target intake (mL/kg/d)*: not stated
Outcomes	Time to regain birth weight Duration of hospitalisation Serum alkaline phosphatase level up to 14 weeks
Identification	**Sponsorship source:** supported in part by a grant from Ross Laboraties, Columbus, Ohio **Setting:** Regional Neonatal Intensive Care Unit, Baptist Medical Center, Montgomery, Alabama, USA (late 1970s)
Notes	Infants were randomised into 3 groups. Only data from group 2 ("standard formula") and group 3 ("nutrient-enriched formula") were included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... randomly allocated..." Randomisation occurred when infants had been weaned from supplemental oxygen and were clinically stable. No further details provided
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome assessments likely to include complete cohort
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Ross Laboratories, the manufacturer of the formula milks used (Osomil and Similac). An employee of Ross Laboratories is acknowledged for having provided "help in statistical data analyses"

Lucas 1989a

Methods	Randomised controlled trial
Participants	Preterm infants weighing < 1850 g at birth (excluding those with "major congenital malformations known to impair growth and development")
Interventions	**Sole diet:** Nutrient-enriched formula (N = 81) • *Energy (kcal/100 mL)*: 80 • *Protein (g/100 mL)*: 2.0 • *Target intake (mL/kg/d)*: 180 Standard formula (N = 79) • *Energy (kcal/100 mL)*: 68 • *Protein (g/100 mL)*: 1.45 • *Target intake (mL/kg/d)*: 180

Outcomes	Rates of change in weight and head circumference (135/160 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g Necrotising enterocolitis - suspected and confirmed reported for complete cohort of 160 infants Bayley Mental Development Index and Psychomotor Development Index at 18 months post term in 114/141 surviving infants Growth parameters in surviving infants (weight, length, and head circumference) at 18 months (119 infants) and at 7.5 to 8 years (135 infants) post term Intelligence quotient at (IQ) at 7.5 to 8 years with abbreviated Weschler Intelligence Scale for Children (revised Anglicised version: WISC-R UK) Bone mineral content (DEXA) at 8 to 12 years Blood pressure and plasma glucose and split proinsulin levels assessed in 31 of 141 (22%) surviving infants at 13 to 16 years
Identification	**Sponsorship source:** Farley Health Products gave financial assistance, continued collaboration, and supply of trial diets **Setting:** Norfolk and Norwich Hospital, Norwich Special Care Baby Unit and Jessop Hospital, Sheffield, UK (early 1980s)
Notes	Investigators reported a parallel trial of the same interventions used as a supplement to human milk (as opposed to use as the sole diet) - see Lucas 1989b

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assignments were based on permuted blocks of variable length" Stratified by birth weight < 1201 g and 1201 to 1850 g Randomised within first 48 hours after birth Randomisation was conducted independently at each centre
Allocation concealment (selection bias)	Low risk	"... sealed envelopes..."; "...consecutively-numbered"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Formulas were identified by numerical code so that neonatal staff, parents, and eventually follow-up staff were blinded to dietary assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Long-term growth and developmental assessments were completed for > 80% of surviving infants Cardiovascular (blood pressure) and metabolic (plasma insulin levels) assessments at age 15 years available for <

		25% enrolled participants
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Farley Health Products, the manufacturer of the formula milks used in this trial, was acknowledged "for their financial assistance, continuing collaboration, and supply of trial diets." It is unclear how far the manufacturer was involved in the conduct of the trial, the statistical analyses, and preparation of the published report

Lucas 1989b

Methods	Randomised controlled trial
Participants	Preterm infants weighing < 1850 g at birth (excluding those with "major congenital malformations known to impair growth and development")
Interventions	**Supplemental to human milk:** Nutrient-enriched formula (N = 132) • *Energy (kcal/100 mL)*: 80 • *Protein (g/100 mL)*: 2.0 • *Target intake (mL/kg/d)*: 180 Standard formula (N = 132) • *Energy (kcal/100 mL)*: 68 • *Protein (g/100 mL)*: 1.45 • *Target intake (mL/kg/d)*: 180
Outcomes	Rates of change in weight and head circumference (225/264 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g Necrotising enterocolitis - suspected and confirmed reported for complete cohort of 264 infants Bayley Mental Development Index and Psychomotor Development Index at 18 months post term in 196/236 surviving infants Growth parameters in surviving infants (weight, length, and head circumference) at 18 months (225 infants) and at 7.5 to 8 years (224 infants) post term Bone mineral content (DEXA) at 8 to 12 years Blood pressure and plasma glucose and split proinsulin levels assessed in 55 of 235 (218%) surviving infants at 13 to 16 years
Identification	**Sponsorship source:** Farley Health Products gave financial assistance, continued collaboration, and supply of trial diets **Setting:** Norfolk and Norwich Hospital, Norwich Special Care Baby Unit and Jessop Hospital, Sheffield, UK (early 1980s)
Notes	Investigators reported a parallel trial of the same interventions used as the sole diet (as opposed to use as a supplement to human milk) - see Lucas 1989a

Lucas 1989b *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Assignments were based on permuted blocks of variable length" Stratified by birth weight < 1201 g and 1201 to 1850 g
Allocation concealment (selection bias)	Low risk	"... sealed envelopes..."; "...consecutively-numbered"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Long-term growth and developmental assessments were completed for > 80% of surviving infants Cardiovascular (blood pressure) and metabolic (plasma insulin levels) assessments at age 15 years available for < 25% of enrolled participants
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Farley Health Products, the manufacturer of the formula milks used in this trial, was acknowledged "for their financial assistance, continuing collaboration, and supply of trial diets." It is unclear how far the manufacturer was involved in the conduct of the trial, the statistical analyses, and preparation of the published report

Siripoonya 1989

Methods	Randomised controlled trial
Participants	Preterm infants weighing 1000 to 1750 g at birth (excluding those with "respiratory distress, infection and other pathology that affected growth and feeding")
Interventions	**Sole diet:** Nutrient-enriched formula (N = 13) • *Energy (kcal/100 mL)*: 80 • *Protein (g/100 mL)*: 2.3 • *Target intake (mL/kg/d)*: 150 Standard formula (N = 12) • *Energy (kcal/100 mL)*: 67 • *Protein (g/100 mL)*: 1.23

	• *Target intake (mL/kg/d)*: 150
Outcomes	Time to regain birth weight and rate of weight gain - calculated from daily weights to the nearest 10 g Rate of length gain and fronto-occipital head circumference measured weekly to the nearest mm
Identification	**Sponsorship source:** supported in part by a grant from Nestle, Switzerland **Setting:** Department of Paediatrics, Mahidol University, Thailand (early-mid 1980s)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 31 preterm infants who were randomised, 6 were excluded due to "illness or infection". No outcome data were reported for these infants, and it is not stated to which group the excluded infants belonged
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Nestle, the manufacturer of the formula milks used in this trial, was the main sponsor

Thom 1984

Methods	Randomised controlled trial
Participants	"Healthy" newborn infants of birth weight < 1501 g
Interventions	**Sole diet:** Nutrient-enriched formula (N = 35) • *Energy (kcal/100 mL)*: 80

	• *Protein (g/100 mL)*: 2.2 • *Target intake (mL/kg/d)*: not stated Standard formula (N = 30) • *Energy (kcal/100 mL)*: 67 • *Protein (g/100 mL)*: 1.23 • *Target intake (mL/kg/d)*: not stated	
Outcomes	Time to regain birth weight Rate of weight, length, and head circumference gain	
Identification	**Sponsorship source:** Nestle Infant and Dietetic Services acknowledged for providing "financial assistance". Further details of sponsorship sources not reported **Setting:** Department of Paediatrics, University of Stellenbosch and Tygerberg Hospital, South Africa (early 1980s)	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"... randomly allocated" - sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 75 randomised infants, 41 were available for assessment at 28 days old
Selective reporting (reporting bias)	High risk	Numerical data not reported for growth outcomes (findings described as "not statistically significant")
Other bias	High risk	The trial was undertaken explicitly to "evaluate this formula [Alprem] clinically". Nestle, the manufacturer of Alprem, is acknowledged for the "supply of Alprem and for financial assistance". It is unclear how the comparator formula (Nan, also manufactured by Nestle) was sourced and how far the manufacturer was involved in the conduct of the trial, the statistical analyses, or production of the publication

Yesilipek 1992

Methods	Randomised controlled trial
Participants	Preterm infants weighing < 2000 g at birth (excluding those with "congenital malformations, infections or respiratory distress syndrome")
Interventions	**Sole diet:** Nutrient-enriched formula (N = 11) • *Energy (kcal/100 mL)*: 81 • *Protein (g/100 mL)*: 1.92 • *Target intake (mL/kg/d)*: 150 Standard formula (N = 11) • *Energy (kcal/100 mL)*: 67 • *Protein (g/100 mL)*: 1.5 • *Target intake (mL/kg/d)*: 150
Outcomes	Rate of weight, length, and head circumference gain
Identification	**Sponsorship source:** not stated **Setting:** Maternity and Children's Hospital, Samsun, Turkey (late 1980s)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomly divided..." - sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome assessments likely to include complete cohort
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funding source not stated

DEXA: dual-energy X-ray absorptiometry.
IQ: intelligence quotient.

WISC-R: Wechsler Intelligence Scale for Children - Revised.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Atkinson 1981	Not an RCT
Duman 2000	Unclear if RCT; none of the formulas used met the definition of "standard"
Haque 1987	Not an RCT
Hering 1987	Intervention formula used did not meet the definition of "nutrient enriched"
Pridham 1999	Term-equivalent infants randomly allocated to nutrient-enriched vs standard formula when nipple-feeding established (> 36 weeks' postmenstrual age)
Yin 2004	Term infants (growth restricted)

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Costa 1996

Methods	Quasi-RCT (birth order alternating allocation to either group)
Participants	Preterm infants (< 37 weeks' gestation) with birth weight < 1750 g (excluding those with serious congenital anomalies, surgical diseases of the gastrointestinal tract, congential infection, and home birth) Subsequent exclusion criteria: change in diet due to team failure; maternal refusal to keep up the regimen up to 40 weeks
Interventions	**Supplemental to human milk:** Nutrient-enriched formula (N = 29: 15 average for gestational age; 14 small for gestational age) • *Energy (kcal/100 mL)*: 81 • *Protein (g/100 mL)*: value not given • *Target intake (mL/kg/d)*: 200 Standard formula (N = 41: 20 average for gestational age; 21 small for gestational age) • *Energy (kcal/100 mL)*: 67 • *Protein (g/100 mL)*: 1.23 • *Target intake (mL/kg/d)*: 200
Outcomes	Time to regain birth weight Rate of weight gain Length gain Head circumference gain

Costa 1996 *(Continued)*

	Feed intolerance
Notes	Awaiting translation and clarification about intervention formula protein content

DATA AND ANALYSES

Comparison 1. Nutrient-enriched formula vs standard formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to regain birth weight	3	74	Mean Difference (IV, Fixed, 95% CI)	-1.48 [-4.73, 1.77]
2 Rate of weight gain (g/kg/d)	6	440	Mean Difference (IV, Fixed, 95% CI)	2.43 [1.60, 3.26]
2.1 Sole diet	5	225	Mean Difference (IV, Fixed, 95% CI)	3.87 [2.26, 5.47]
2.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	1.90 [0.93, 2.87]
3 Rate of length gain (mm/week)	5	386	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.70, 1.13]
3.1 Sole diet	4	185	Mean Difference (IV, Fixed, 95% CI)	1.72 [0.23, 3.20]
3.2 Supplemental to human milk	1	201	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.86, 0.46]
4 Rate of head circumference gain (mm/week)	5	399	Mean Difference (IV, Fixed, 95% CI)	1.04 [0.18, 1.89]
4.1 Sole diet	4	184	Mean Difference (IV, Fixed, 95% CI)	2.26 [1.00, 3.52]
4.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.16, 1.16]
5 Rate of skinfold thickness gain - triceps (mm/week)	4	364	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.07, 0.17]
5.1 Sole diet	3	163	Mean Difference (IV, Fixed, 95% CI)	0.16 [0.05, 0.27]
5.2 Supplemental to human milk	1	201	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.05, 0.17]
6 Rate of skinfold thickness gain - subscapular (mm/week)	3	339	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.04, 0.16]
6.1 Sole diet	2	138	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.07, 0.24]
6.2 Supplemental to human milk	1	201	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.02, 0.14]
7 Weight (kg) at 18 months post term	2	334	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.21, 0.33]
7.1 Sole diet	1	119	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.31, 0.71]
7.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.32, 0.32]
8 Weight (kg) at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.55, 1.15]
8.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.99, 1.59]
8.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.84, 1.44]
9 Height (cm) at 18 months post term	2	334	Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.43, 1.06]
9.1 Sole diet	1	119	Mean Difference (IV, Fixed, 95% CI)	1.20 [-0.26, 2.66]
9.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.87, 0.87]
10 Height (cm) at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	0.93 [-0.30, 2.16]
10.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.69, 3.29]

10.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.86, 2.26]
11 Head circumference (cm) at 18 months post term	2	334	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.26, 0.43]
11.1 Sole diet	1	119	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.32, 0.72]
11.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.45, 0.45]
12 Head circumference (cm) at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.45, 0.21]
12.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.52, 0.52]
12.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.62, 0.22]
13 Triceps skinfold thickness (mm) at 18 months post term	2	334	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.42, 0.45]
13.1 Sole diet	1	119	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.50, 0.90]
13.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.65, 0.45]
14 Triceps skinfold thickness (mm) at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.91, 0.60]
14.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.85, 1.45]
14.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.50, 0.50]
15 Subscapular skinfold thickness (mm) at 18 months post term	2	334	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.40, 0.13]
15.1 Sole diet	1	119	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.47, 0.47]
15.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.52, 0.12]
16 Subscapular skinfold thickness (mm) at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.67, 0.57]
16.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.96, 0.76]
16.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.90, 0.90]
17 Cerebral palsy at 18 months post term	2	377	Risk Ratio (IV, Fixed, 95% CI)	0.79 [0.30, 2.07]
17.1 Sole diet	1	141	Risk Ratio (IV, Fixed, 95% CI)	0.51 [0.05, 5.47]
17.2 Supplemental to human milk	1	236	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.30, 2.47]
18 Bayley (1) Mental Development Index at 18 months post term	2	310	Mean Difference (IV, Fixed, 95% CI)	2.81 [-1.44, 7.06]
18.1 Sole diet	1	114	Mean Difference (IV, Fixed, 95% CI)	6.0 [-1.07, 13.07]
18.2 Supplemental to human milk	1	196	Mean Difference (IV, Fixed, 95% CI)	1.0 [-4.32, 6.32]
19 Weschler Verbal Intelligence Quotient at 7.5 to 8 years post term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Sole diet	1	133	Mean Difference (IV, Fixed, 95% CI)	4.90 [-0.38, 10.18]
19.2 Supplemental to human milk	1	222	Mean Difference (IV, Fixed, 95% CI)	0.30 [-4.41, 5.01]

20 Bayley (1) Psychomotor Development Index at 18 months post term	2	310	Mean Difference (IV, Fixed, 95% CI)	6.56 [2.87, 10.26]
20.1 Sole diet	1	114	Mean Difference (IV, Fixed, 95% CI)	14.70 [8.73, 20.67]
20.2 Supplemental to human milk	1	196	Mean Difference (IV, Fixed, 95% CI)	1.5 [-3.20, 6.20]
21 Weschler Performance Intelligence Quotient at 7.5 to 8 years post term	2	355	Mean Difference (IV, Fixed, 95% CI)	0.06 [-3.24, 3.36]
21.1 Sole diet	1	133	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-7.12, 3.72]
21.2 Supplemental to human milk	1	222	Mean Difference (IV, Fixed, 95% CI)	1.10 [-3.06, 5.26]
22 Weschler Overall Intelligence Quotient at 7.5 to 8 years post term	2	355	Mean Difference (IV, Fixed, 95% CI)	1.49 [-1.61, 4.59]
22.1 Sole diet	1	133	Mean Difference (IV, Fixed, 95% CI)	2.20 [-2.65, 7.05]
22.2 Supplemental to human milk	1	222	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.03, 5.03]
23 Necrotising enterocolitis	3	489	Risk Ratio (IV, Fixed, 95% CI)	0.72 [0.41, 1.25]
23.1 Sole diet	2	225	Risk Ratio (IV, Fixed, 95% CI)	0.67 [0.27, 1.65]
23.2 Supplemental to human milk	1	264	Risk Ratio (IV, Fixed, 95% CI)	0.75 [0.37, 1.52]
24 Duration of birth hospitalisation	1	31	Mean Difference (IV, Fixed, 95% CI)	1.0 [-8.81, 10.81]
25 All-cause mortality	2	424	Risk Ratio (IV, Fixed, 95% CI)	1.12 [0.65, 1.93]
25.1 Sole diet	1	160	Risk Ratio (IV, Fixed, 95% CI)	1.34 [0.57, 3.16]
25.2 Supplemental to human milk	1	264	Risk Ratio (IV, Fixed, 95% CI)	1.0 [0.50, 2.01]
26 Body mass index (kg/m²) at 18 months post term	2	334	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.43, 0.23]
26.1 Sole diet	1	119	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.70, 0.50]
26.2 Supplemental to human milk	1	215	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.50, 0.30]
27 Body mass index (kg/m²) at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.33, 0.44]
27.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.57, 0.57]
27.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.41, 0.61]
28 Waist-to-hip ratio at 7.5 to 8 years post term	2	359	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.16, 0.12]
28.1 Sole diet	1	135	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.20, 0.14]
28.2 Supplemental to human milk	1	224	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.26, 0.28]
29 Serum alkaline phosphatase level after 4 weeks (IU/mL)	2	49	Mean Difference (IV, Fixed, 95% CI)	-41.12 [-86.89, 4.65]
30 Bone mineral content (g) assessed by DEXA at 8 to 12 years	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
30.1 Lumbar spine	1	61	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-5.62, 0.22]
30.2 Femoral neck	1	61	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.19, 0.39]
30.3 Radius	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.02]

30.4 Whole body	1	60	Mean Difference (IV, Fixed, 95% CI)	-77.0 [-777.29, 623.29]

Analysis 1.1. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 1 Time to regain birth weight.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

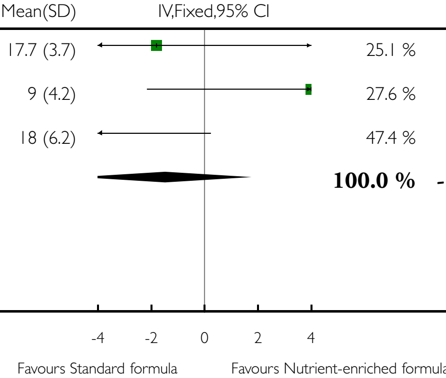
Outcome: 1 Time to regain birth weight

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kashyap 1986	9	15.9 (9.2)	9	17.7 (3.7)		25.1 %	-1.80 [-8.28, 4.68]
Kulkarni 1984	13	13 (10.8)	18	9 (4.2)		27.6 %	4.00 [-2.18, 10.18]
Siripoonya 1989	13	13.5 (5.8)	12	18 (6.2)		47.4 %	-4.50 [-9.22, 0.22]
Total (95% CI)	**35**		**39**			**100.0 %**	**-1.48 [-4.73, 1.77]**

Heterogeneity: $Chi^2 = 4.60$, df = 2 (P = 0.10); $I^2 = 57\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



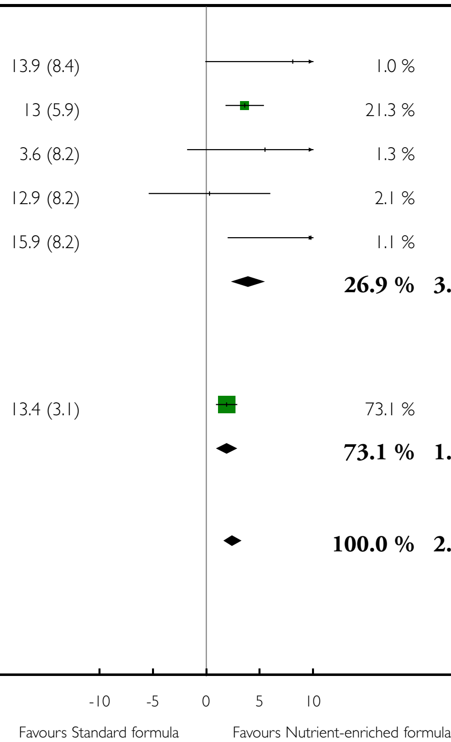
Analysis 1.2. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 2 Rate of weight gain (g/kg/d).

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 2 Rate of weight gain (g/kg/d)

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Kashyap 1986	9	22 (9.3)	9	13.9 (8.4)		1.0 %	8.10 [-0.09, 16.29]
Lucas 1989a	61	16.6 (3.9)	58	13 (5.9)		21.3 %	3.60 [1.79, 5.41]
Siripoonya 1989	13	9.1 (10.4)	12	3.6 (8.2)		1.3 %	5.50 [-1.81, 12.81]
Thom 1984	21	13.2 (10.4)	20	12.9 (8.2)		2.1 %	0.30 [-5.42, 6.02]
Yesilipek 1992	11	25.7 (10.4)	11	15.9 (8.2)		1.1 %	9.80 [1.97, 17.63]
Subtotal (95% CI)	**115**		**110**			**26.9 %**	**3.87 [2.26, 5.47]**
Heterogeneity: $Chi^2 = 5.00$, df = 4 (P = 0.29); $I^2 = 20\%$							
Test for overall effect: Z = 4.71 (P < 0.00001)							
2 Supplemental to human milk							
Lucas 1989b	105	15.3 (4.1)	110	13.4 (3.1)		73.1 %	1.90 [0.93, 2.87]
Subtotal (95% CI)	**105**		**110**			**73.1 %**	**1.90 [0.93, 2.87]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.82 (P = 0.00013)							
Total (95% CI)	**220**		**220**			**100.0 %**	**2.43 [1.60, 3.26]**
Heterogeneity: $Chi^2 = 9.21$, df = 5 (P = 0.10); $I^2 = 46\%$							
Test for overall effect: Z = 5.71 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 4.20$, df = 1 (P = 0.04), $I^2 = 76\%$							



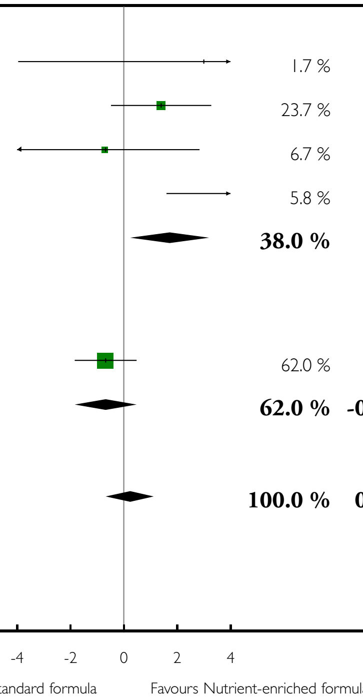
Analysis 1.3. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 3 Rate of length gain (mm/week).

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 3 Rate of length gain (mm/week)

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Kashyap 1986	9	12.4 (9)	9	9.4 (5.7)		1.7 %	3.00 [-3.96, 9.96]
Lucas 1989a	61	10.5 (5.6)	59	9.1 (4.9)		23.7 %	1.40 [-0.48, 3.28]
Siripoonya 1989	13	8 (5.3)	12	8.7 (3.6)		6.7 %	-0.70 [-4.23, 2.83]
Yesilipek 1992	11	16.3 (5.3)	11	10.9 (3.6)		5.8 %	5.40 [1.61, 9.19]
Subtotal (95% CI)	**94**		**91**			**38.0 %**	**1.72 [0.23, 3.20]**
Heterogeneity: $Chi^2 = 5.68$, df = 3 (P = 0.13); I^2 =47%							
Test for overall effect: Z = 2.26 (P = 0.024)							
2 Supplemental to human milk							
Lucas 1989b	103	9.1 (4.2)	98	9.8 (4.2)		62.0 %	-0.70 [-1.86, 0.46]
Subtotal (95% CI)	**103**		**98**			**62.0 %**	**-0.70 [-1.86, 0.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.18 (P = 0.24)							
Total (95% CI)	**197**		**189**			**100.0 %**	**0.22 [-0.70, 1.13]**
Heterogeneity: $Chi^2 = 11.99$, df = 4 (P = 0.02); I^2 =67%							
Test for overall effect: Z = 0.47 (P = 0.64)							
Test for subgroup differences: $Chi^2 = 6.31$, df = 1 (P = 0.01), I^2 =84%							



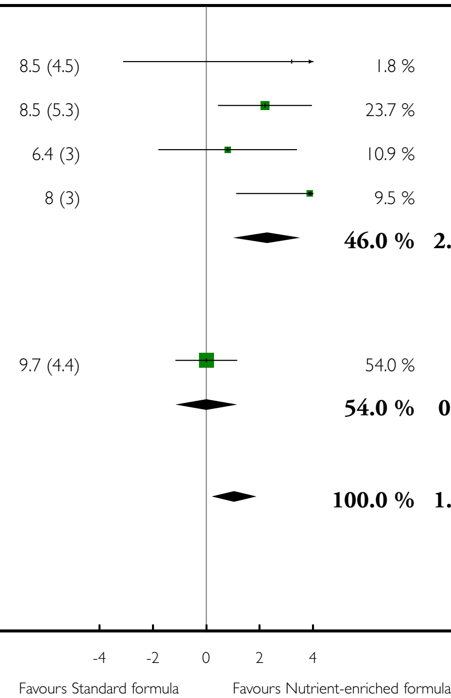
Analysis 1.4. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 4 Rate of head circumference gain (mm/week).

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 4 Rate of head circumference gain (mm/week)

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Kashyap 1986	9	11.7 (8.6)	9	8.5 (4.5)		1.8 %	3.20 [-3.14, 9.54]
Lucas 1989a	61	10.7 (4.4)	58	8.5 (5.3)		23.7 %	2.20 [0.45, 3.95]
Siripoonya 1989	13	7.2 (3.6)	12	6.4 (3)		10.9 %	0.80 [-1.79, 3.39]
Yesilipek 1992	11	11.9 (3.6)	11	8 (3)		9.5 %	3.90 [1.13, 6.67]
Subtotal (95% CI)	**94**		**90**			**46.0 %**	**2.26 [1.00, 3.52]**
Heterogeneity: Chi^2 = 2.66, df = 3 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 3.51 (P = 0.00044)							
2 Supplemental to human milk							
Lucas 1989b	105	9.7 (4.3)	110	9.7 (4.4)		54.0 %	0.0 [-1.16, 1.16]
Subtotal (95% CI)	**105**		**110**			**54.0 %**	**0.0 [-1.16, 1.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**199**		**200**			**100.0 %**	**1.04 [0.18, 1.89]**
Heterogeneity: Chi^2 = 9.33, df = 4 (P = 0.05); I^2 =57%							
Test for overall effect: Z = 2.38 (P = 0.017)							
Test for subgroup differences: Chi^2 = 6.67, df = 1 (P = 0.01), I^2 =85%							



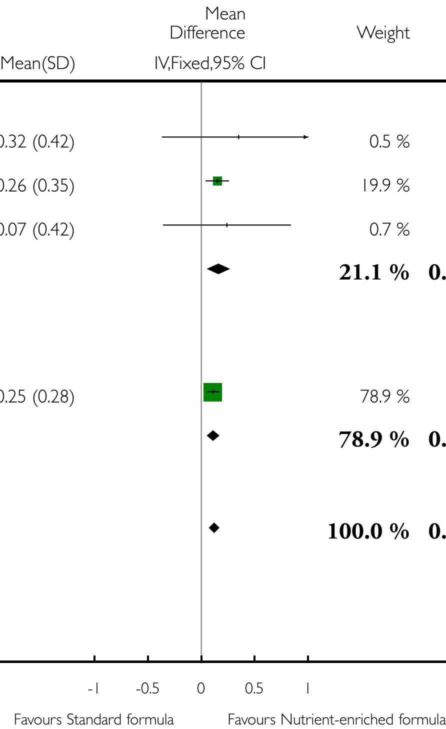
Analysis 1.5. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 5 Rate of skinfold thickness gain - triceps (mm/week).

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 5 Rate of skinfold thickness gain - triceps (mm/week)

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet						
Kashyap 1986	9	0.67 (1.02)	9	0.32 (0.42)	0.5 %	0.35 [-0.37, 1.07]
Lucas 1989a	61	0.41 (0.28)	59	0.26 (0.35)	19.9 %	0.15 [0.04, 0.26]
Siripoonya 1989	13	0.31 (1.02)	12	0.07 (0.42)	0.7 %	0.24 [-0.36, 0.84]
Subtotal (95% CI)	**83**		**80**		**21.1 %**	**0.16 [0.05, 0.27]**
Heterogeneity: $Chi^2 = 0.36$, df = 2 (P = 0.83); I^2 =0.0%						
Test for overall effect: Z = 2.80 (P = 0.0051)						
2 Supplemental to human milk						
Lucas 1989b	103	0.36 (0.07)	98	0.25 (0.28)	78.9 %	0.11 [0.05, 0.17]
Subtotal (95% CI)	**103**		**98**		**78.9 %**	**0.11 [0.05, 0.17]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.78 (P = 0.00016)						
Total (95% CI)	**186**		**178**		**100.0 %**	**0.12 [0.07, 0.17]**
Heterogeneity: $Chi^2 = 0.93$, df = 3 (P = 0.82); I^2 =0.0%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.57$, df = 1 (P = 0.45), I^2 =0.0%						



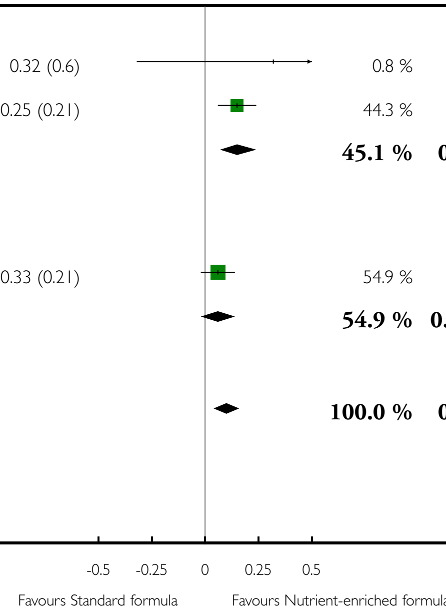
Analysis 1.6. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 6 Rate of skinfold thickness gain - subscapular (mm/week).

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 6 Rate of skinfold thickness gain - subscapular (mm/week)

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Kashyap 1986	9	0.64 (0.78)	9	0.32 (0.6)		0.8 %	0.32 [-0.32, 0.96]
Lucas 1989a	61	0.4 (0.28)	59	0.25 (0.21)		44.3 %	0.15 [0.06, 0.24]
Subtotal (95% CI)	**70**		**68**			**45.1 %**	**0.15 [0.07, 0.24]**
Heterogeneity: $Chi^2 = 0.26$, df = 1 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 3.43 (P = 0.00061)							
2 Supplemental to human milk							
Lucas 1989b	103	0.39 (0.35)	98	0.33 (0.21)		54.9 %	0.06 [-0.02, 0.14]
Subtotal (95% CI)	**103**		**98**			**54.9 %**	**0.06 [-0.02, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Total (95% CI)	**173**		**166**			**100.0 %**	**0.10 [0.04, 0.16]**
Heterogeneity: $Chi^2 = 2.65$, df = 2 (P = 0.27); I^2 =25%							
Test for overall effect: Z = 3.40 (P = 0.00067)							
Test for subgroup differences: $Chi^2 = 2.39$, df = 1 (P = 0.12), I^2 =58%							



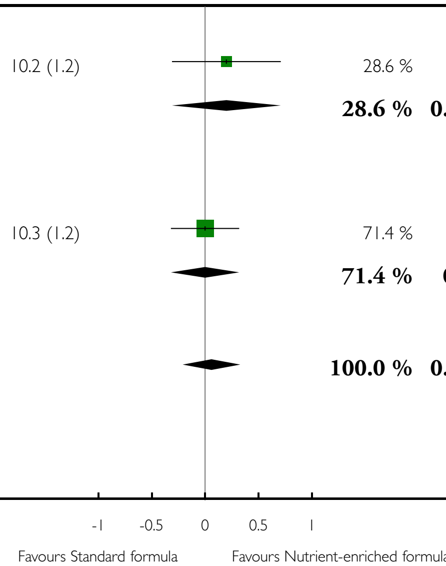
Analysis 1.7. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 7 Weight (kg) at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 7 Weight (kg) at 18 months post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	61	10.4 (1.6)	58	10.2 (1.2)		28.6 %	0.20 [-0.31, 0.71]
Subtotal (95% CI)	**61**		**58**			**28.6 %**	**0.20 [-0.31, 0.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							
2 Supplemental to human milk							
Lucas 1989b	105	10.3 (1.2)	110	10.3 (1.2)		71.4 %	0.0 [-0.32, 0.32]
Subtotal (95% CI)	**105**		**110**			**71.4 %**	**0.0 [-0.32, 0.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**166**		**168**			**100.0 %**	**0.06 [-0.21, 0.33]**
Heterogeneity: Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%							
Test for overall effect: Z = 0.41 (P = 0.68)							
Test for subgroup differences: Chi^2 = 0.43, df = 1 (P = 0.51), I^2 =0.0%							



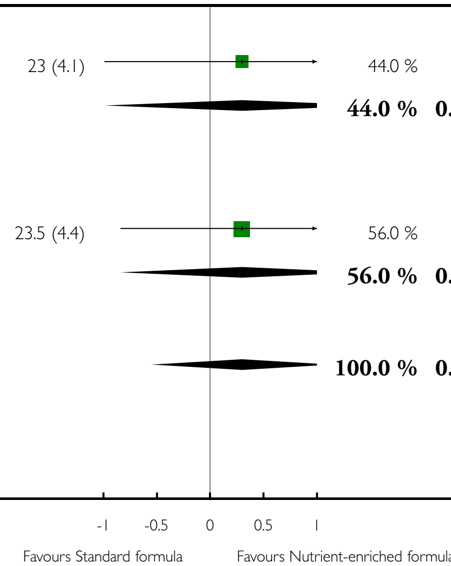
Analysis 1.8. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 8 Weight (kg) at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 8 Weight (kg) at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	67	23.3 (3.5)	68	23 (4.1)		44.0 %	0.30 [-0.99, 1.59]
Subtotal (95% CI)	**67**		**68**			**44.0 %**	**0.30 [-0.99, 1.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							
2 Supplemental to human milk							
Lucas 1989b	111	23.8 (4.3)	113	23.5 (4.4)		56.0 %	0.30 [-0.84, 1.44]
Subtotal (95% CI)	**111**		**113**			**56.0 %**	**0.30 [-0.84, 1.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.52 (P = 0.61)							
Total (95% CI)	**178**		**181**			**100.0 %**	**0.30 [-0.55, 1.15]**
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.69 (P = 0.49)							
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 1.00), $I^2 = 0.0\%$							



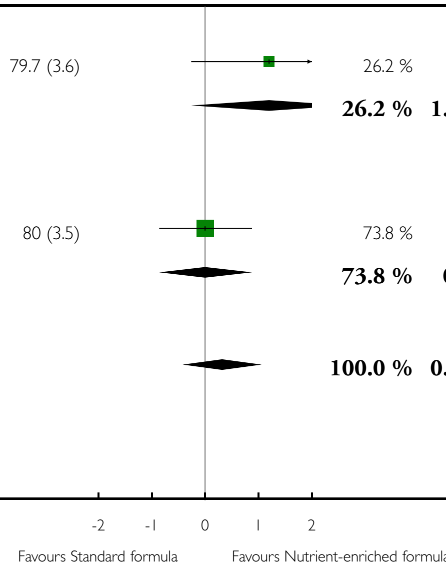
Analysis 1.9. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 9 Height (cm) at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 9 Height (cm) at 18 months post term

Study or subgroup	Nutrient-enriched formula		Standard formula		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	61	80.9 (4.5)	58	79.7 (3.6)		26.2 %	1.20 [-0.26, 2.66]
Subtotal (95% CI)	**61**		**58**			**26.2 %**	**1.20 [-0.26, 2.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.61 (P = 0.11)							
2 Supplemental to human milk							
Lucas 1989b	105	80 (3)	110	80 (3.5)		73.8 %	0.0 [-0.87, 0.87]
Subtotal (95% CI)	**105**		**110**			**73.8 %**	**0.0 [-0.87, 0.87]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**166**		**168**			**100.0 %**	**0.31 [-0.43, 1.06]**
Heterogeneity: Chi^2 = 1.91, df = 1 (P = 0.17); I^2 =48%							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Chi^2 = 1.91, df = 1 (P = 0.17), I^2 =48%							



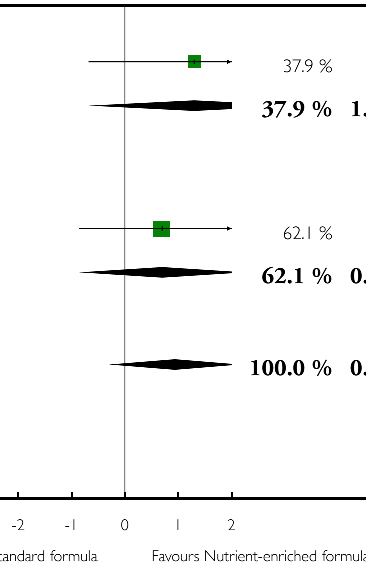
Analysis 1.10. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 10 Height (cm) at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 10 Height (cm) at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	67	122.9 (5.5)	68	121.6 (6.3)		37.9 %	1.30 [-0.69, 3.29]
Subtotal (95% CI)	**67**		**68**			**37.9 %**	**1.30 [-0.69, 3.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.28 (P = 0.20)							
2 Supplemental to human milk							
Lucas 1989b	111	123.2 (5.9)	113	122.5 (6)		62.1 %	0.70 [-0.86, 2.26]
Subtotal (95% CI)	**111**		**113**			**62.1 %**	**0.70 [-0.86, 2.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.88 (P = 0.38)							
Total (95% CI)	**178**		**181**			**100.0 %**	**0.93 [-0.30, 2.16]**
Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%							
Test for overall effect: Z = 1.48 (P = 0.14)							
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%							



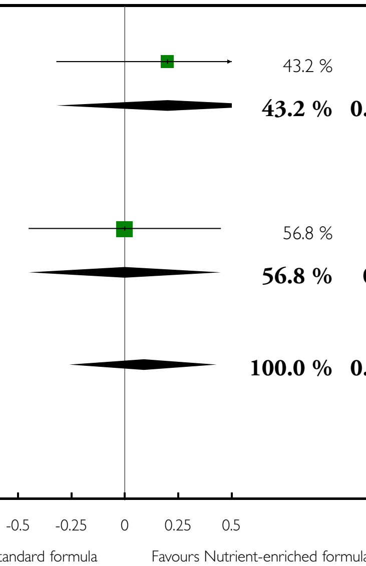
Analysis 1.11. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 11 Head circumference (cm) at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 11 Head circumference (cm) at 18 months post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	61	47.7 (1.5)	58	47.5 (1.4)		43.2 %	0.20 [-0.32, 0.72]
Subtotal (95% CI)	**61**		**58**			**43.2 %**	**0.20 [-0.32, 0.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.75 (P = 0.45)							
2 Supplemental to human milk							
Lucas 1989b	105	48.1 (1.6)	110	48.1 (1.8)		56.8 %	0.0 [-0.45, 0.45]
Subtotal (95% CI)	**105**		**110**			**56.8 %**	**0.0 [-0.45, 0.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**166**		**168**			**100.0 %**	**0.09 [-0.26, 0.43]**
Heterogeneity: $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.49 (P = 0.62)							
Test for subgroup differences: $Chi^2 = 0.32$, df = 1 (P = 0.57), $I^2 = 0.0\%$							



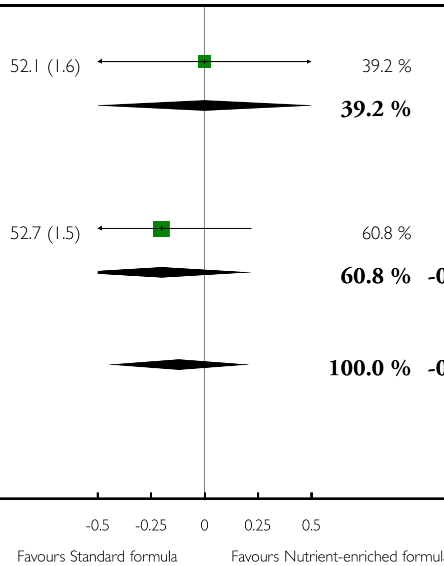
Analysis 1.12. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 12 Head circumference (cm) at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 12 Head circumference (cm) at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	67	52.1 (1.5)	68	52.1 (1.6)		39.2 %	0.0 [-0.52, 0.52]
Subtotal (95% CI)	**67**		**68**			**39.2 %**	**0.0 [-0.52, 0.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 Supplemental to human milk							
Lucas 1989b	111	52.5 (1.7)	113	52.7 (1.5)		60.8 %	-0.20 [-0.62, 0.22]
Subtotal (95% CI)	**111**		**113**			**60.8 %**	**-0.20 [-0.62, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.93 (P = 0.35)							
Total (95% CI)	**178**		**181**			**100.0 %**	**-0.12 [-0.45, 0.21]**
Heterogeneity: $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.73 (P = 0.47)							
Test for subgroup differences: $Chi^2 = 0.34$, df = 1 (P = 0.56), $I^2 = 0.0\%$							



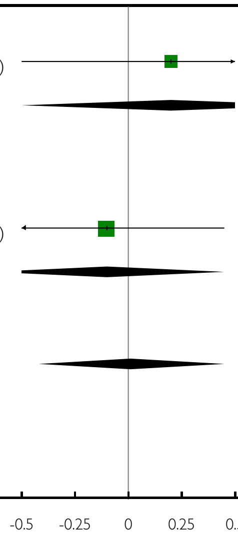
Analysis 1.13. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 13 Triceps skinfold thickness (mm) at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 13 Triceps skinfold thickness (mm) at 18 months post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	61	8.4 (2.1)	58	8.2 (1.8)		38.1 %	0.20 [-0.50, 0.90]
Subtotal (95% CI)	**61**		**58**			**38.1 %**	**0.20 [-0.50, 0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.56 (P = 0.58)							
2 Supplemental to human milk							
Lucas 1989b	105	8.1 (2.2)	110	8.2 (1.9)		61.9 %	-0.10 [-0.65, 0.45]
Subtotal (95% CI)	**105**		**110**			**61.9 %**	**-0.10 [-0.65, 0.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.36 (P = 0.72)							
Total (95% CI)	**166**		**168**			**100.0 %**	**0.01 [-0.42, 0.45]**
Heterogeneity: Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%							
Test for overall effect: Z = 0.06 (P = 0.95)							
Test for subgroup differences: Chi^2 = 0.43, df = 1 (P = 0.51), I^2 =0.0%							



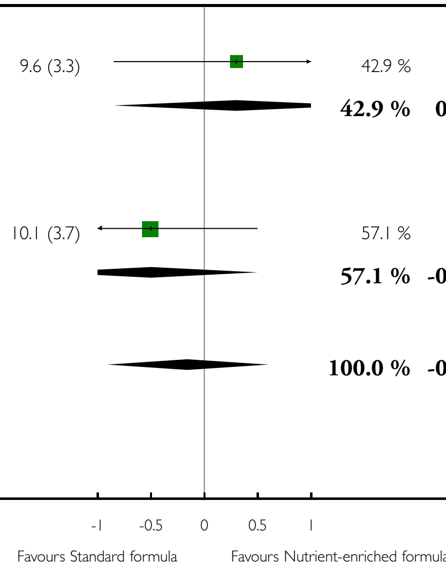
Analysis 1.14. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 14 Triceps skinfold thickness (mm) at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 14 Triceps skinfold thickness (mm) at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	67	9.9 (3.5)	68	9.6 (3.3)		42.9 %	0.30 [-0.85, 1.45]
Subtotal (95% CI)	**67**		**68**			**42.9 %**	**0.30 [-0.85, 1.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.51 (P = 0.61)							
2 Supplemental to human milk							
Lucas 1989b	111	9.6 (3.9)	113	10.1 (3.7)		57.1 %	-0.50 [-1.50, 0.50]
Subtotal (95% CI)	**111**		**113**			**57.1 %**	**-0.50 [-1.50, 0.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
Total (95% CI)	**178**		**181**			**100.0 %**	**-0.16 [-0.91, 0.60]**
Heterogeneity: Chi^2 = 1.06, df = 1 (P = 0.30); I^2 =6%							
Test for overall effect: Z = 0.41 (P = 0.68)							
Test for subgroup differences: Chi^2 = 1.06, df = 1 (P = 0.30), I^2 =6%							



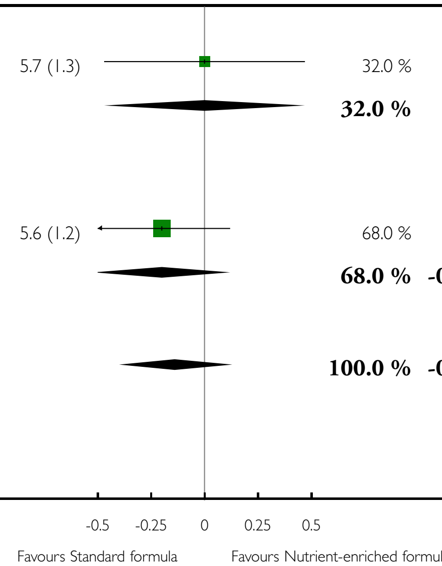
Analysis 1.15. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 15 Subscapular skinfold thickness (mm) at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 15 Subscapular skinfold thickness (mm) at 18 months post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	61	5.7 (1.3)	58	5.7 (1.3)		32.0 %	0.0 [-0.47, 0.47]
Subtotal (95% CI)	**61**		**58**			**32.0 %**	**0.0 [-0.47, 0.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 Supplemental to human milk							
Lucas 1989b	105	5.4 (1.2)	110	5.6 (1.2)		68.0 %	-0.20 [-0.52, 0.12]
Subtotal (95% CI)	**105**		**110**			**68.0 %**	**-0.20 [-0.52, 0.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.22 (P = 0.22)							
Total (95% CI)	**166**		**168**			**100.0 %**	**-0.14 [-0.40, 0.13]**
Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 1.01 (P = 0.31)							
Test for subgroup differences: Chi^2 = 0.48, df = 1 (P = 0.49), I^2 =0.0%							



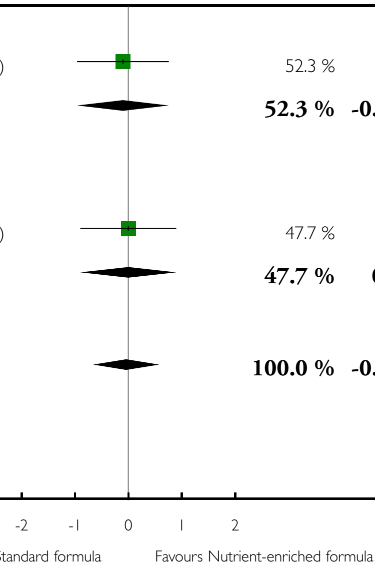
Analysis 1.16. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 16 Subscapular skinfold thickness (mm) at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 16 Subscapular skinfold thickness (mm) at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet						
Lucas 1989a	67	6.3 (2.4)	68	6.4 (2.7)	52.3 %	-0.10 [-0.96, 0.76]
Subtotal (95% CI)	**67**		**68**		**52.3 %**	**-0.10 [-0.96, 0.76]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
2 Supplemental to human milk						
Lucas 1989b	111	6.4 (3.9)	113	6.4 (2.9)	47.7 %	0.0 [-0.90, 0.90]
Subtotal (95% CI)	**111**		**113**		**47.7 %**	**0.0 [-0.90, 0.90]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
Total (95% CI)	**178**		**181**		**100.0 %**	**-0.05 [-0.67, 0.57]**
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%						



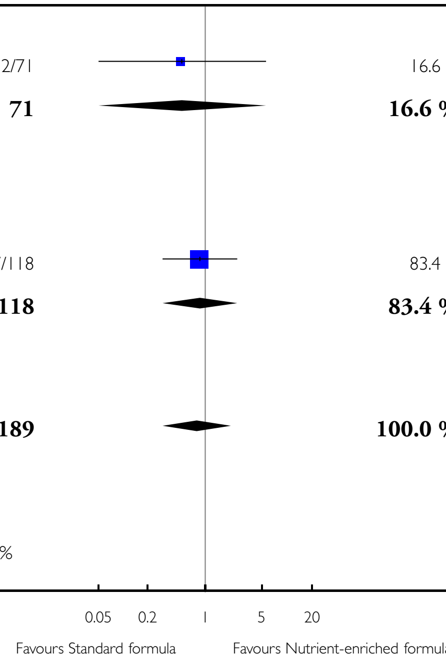
Analysis 1.17. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 17 Cerebral palsy at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 17 Cerebral palsy at 18 months post term

Study or subgroup	Nutrient-enriched formula n/N	Standard formula n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Sole diet					
Lucas 1989a	1/70	2/71		16.6 %	0.51 [0.05, 5.47]
Subtotal (95% CI)	**70**	**71**		**16.6 %**	**0.51 [0.05, 5.47]**
Total events: 1 (Nutrient-enriched formula), 2 (Standard formula)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					
2 Supplemental to human milk					
Lucas 1989b	6/118	7/118		83.4 %	0.86 [0.30, 2.47]
Subtotal (95% CI)	**118**	**118**		**83.4 %**	**0.86 [0.30, 2.47]**
Total events: 6 (Nutrient-enriched formula), 7 (Standard formula)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.28 (P = 0.78)					
Total (95% CI)	**188**	**189**		**100.0 %**	**0.79 [0.30, 2.07]**
Total events: 7 (Nutrient-enriched formula), 9 (Standard formula)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.49 (P = 0.63)					
Test for subgroup differences: Chi^2 = 0.16, df = 1 (P = 0.69), I^2 =0.0%					



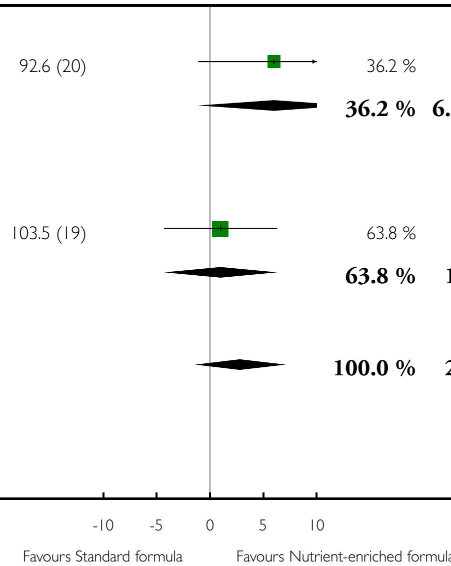
Analysis 1.18. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 18 Bayley (1) Mental Development Index at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 18 Bayley (1) Mental Development Index at 18 months post term

Study or subgroup	Standard formula N	Standard formula Mean(SD)	Nutrient-enriched formula N	Nutrient-enriched formula Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	59	98.6 (18.4)	55	92.6 (20)		36.2 %	6.00 [-1.07, 13.07]
Subtotal (95% CI)	**59**		**55**			**36.2 %**	**6.00 [-1.07, 13.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.66 (P = 0.096)							
2 Supplemental to human milk							
Lucas 1989b	95	104.5 (19)	101	103.5 (19)		63.8 %	1.00 [-4.32, 6.32]
Subtotal (95% CI)	**95**		**101**			**63.8 %**	**1.00 [-4.32, 6.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
Total (95% CI)	**154**		**156**			**100.0 %**	**2.81 [-1.44, 7.06]**
Heterogeneity: Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =18%							
Test for overall effect: Z = 1.29 (P = 0.20)							
Test for subgroup differences: Chi^2 = 1.23, df = 1 (P = 0.27), I^2 =18%							



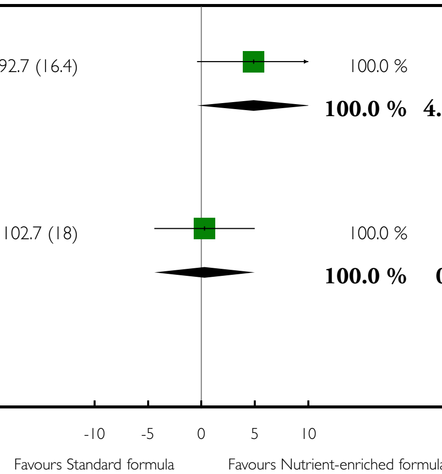
Analysis 1.19. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 19 Weschler Verbal Intelligence Quotient at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 19 Weschler Verbal Intelligence Quotient at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	66	97.6 (14.6)	67	92.7 (16.4)		100.0 %	4.90 [-0.38, 10.18]
Subtotal (95% CI)	**66**		**67**			**100.0 %**	**4.90 [-0.38, 10.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.82 (P = 0.069)							
2 Supplemental to human milk							
Lucas 1989b	110	103 (17.8)	112	102.7 (18)		100.0 %	0.30 [-4.41, 5.01]
Subtotal (95% CI)	**110**		**112**			**100.0 %**	**0.30 [-4.41, 5.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.12 (P = 0.90)							
Test for subgroup differences: Chi^2 = 1.63, df = 1 (P = 0.20), I^2 =38%							



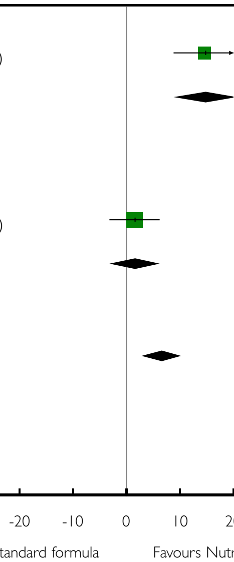
Analysis 1.20. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 20 Bayley (1) Psychomotor Development Index at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 20 Bayley (1) Psychomotor Development Index at 18 months post term

Study or subgroup	Standard formula N	Mean(SD)	Nutrient-enriched formula N	Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet						
Lucas 1989a	59	98.9 (16.9)	55	84.2 (15.6)	38.3 %	14.70 [8.73, 20.67]
Subtotal (95% CI)	**59**		**55**		**38.3 %**	**14.70 [8.73, 20.67]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.83 (P < 0.00001)						
2 Supplemental to human milk						
Lucas 1989b	95	94 (16.6)	101	92.5 (17)	61.7 %	1.50 [-3.20, 6.20]
Subtotal (95% CI)	**95**		**101**		**61.7 %**	**1.50 [-3.20, 6.20]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
Total (95% CI)	**154**		**156**		**100.0 %**	**6.56 [2.87, 10.26]**
Heterogeneity: Chi^2 = 11.59, df = 1 (P = 0.00066); I^2 =91%						
Test for overall effect: Z = 3.48 (P = 0.00050)						
Test for subgroup differences: Chi^2 = 11.59, df = 1 (P = 0.00), I^2 =91%						



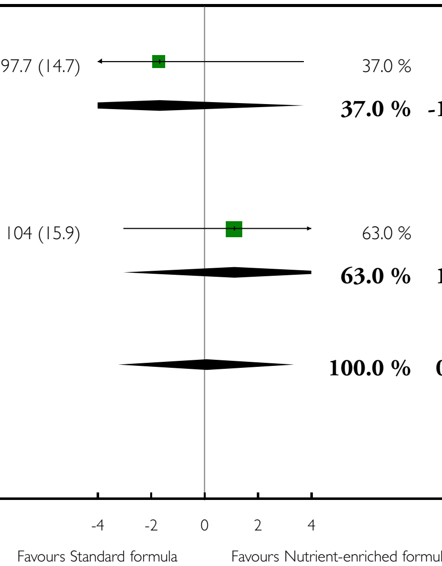
Analysis 1.21. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 21 Weschler Performance Intelligence Quotient at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 21 Weschler Performance Intelligence Quotient at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	66	96 (17.1)	67	97.7 (14.7)		37.0 %	-1.70 [-7.12, 3.72]
Subtotal (95% CI)	**66**		**67**			**37.0 %**	**-1.70 [-7.12, 3.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
2 Supplemental to human milk							
Lucas 1989b	110	105.1 (15.7)	112	104 (15.9)		63.0 %	1.10 [-3.06, 5.26]
Subtotal (95% CI)	**110**		**112**			**63.0 %**	**1.10 [-3.06, 5.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.52 (P = 0.60)							
Total (95% CI)	**176**		**179**			**100.0 %**	**0.06 [-3.24, 3.36]**
Heterogeneity: Chi^2 = 0.65, df = 1 (P = 0.42); I^2 =0.0%							
Test for overall effect: Z = 0.04 (P = 0.97)							
Test for subgroup differences: Chi^2 = 0.65, df = 1 (P = 0.42), I^2 =0.0%							



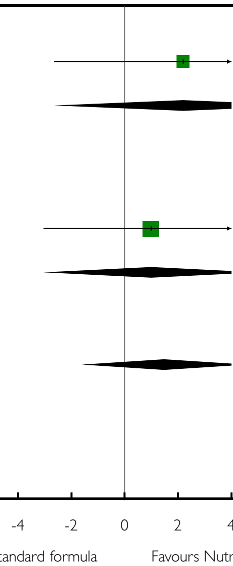
Analysis 1.22. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 22 Weschler Overall Intelligence Quotient at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 22 Weschler Overall Intelligence Quotient at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	66	97 (14.6)	67	94.8 (13.9)		40.8 %	2.20 [-2.65, 7.05]
Subtotal (95% CI)	**66**		**67**			**40.8 %**	**2.20 [-2.65, 7.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.89 (P = 0.37)							
2 Supplemental to human milk							
Lucas 1989b	110	104.2 (14.7)	112	103.2 (15.9)		59.2 %	1.00 [-3.03, 5.03]
Subtotal (95% CI)	**110**		**112**			**59.2 %**	**1.00 [-3.03, 5.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.63)							
Total (95% CI)	**176**		**179**			**100.0 %**	**1.49 [-1.61, 4.59]**
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 0.94 (P = 0.35)							
Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.71), I^2 =0.0%							



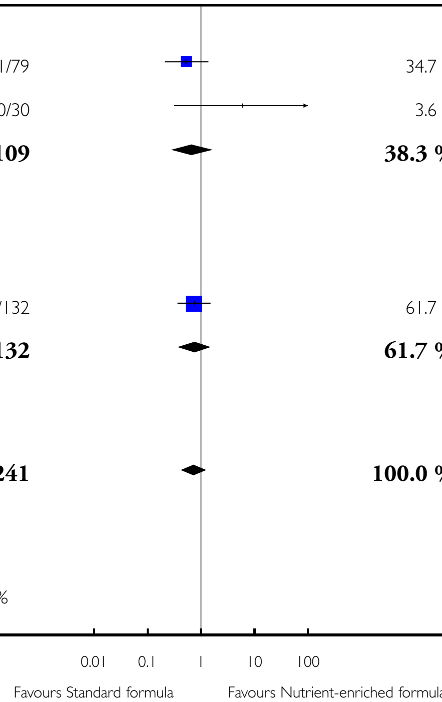
Analysis 1.23. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 23 Necrotising enterocolitis.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 23 Necrotising enterocolitis

Study or subgroup	Nutrient-enriched formula n/N	Standard formula n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Sole diet					
Lucas 1989a	6/81	11/79		34.7 %	0.53 [0.21, 1.37]
Thom 1984	3/35	0/30		3.6 %	6.03 [0.32, 112.21]
Subtotal (95% CI)	**116**	**109**		**38.3 %**	**0.67 [0.27, 1.65]**
Total events: 9 (Nutrient-enriched formula), 11 (Standard formula)					
Heterogeneity: $Chi^2 = 2.40$, df = 1 (P = 0.12); I^2 =58%					
Test for overall effect: Z = 0.87 (P = 0.38)					
2 Supplemental to human milk					
Lucas 1989b	12/132	16/132		61.7 %	0.75 [0.37, 1.52]
Subtotal (95% CI)	**132**	**132**		**61.7 %**	**0.75 [0.37, 1.52]**
Total events: 12 (Nutrient-enriched formula), 16 (Standard formula)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.43)					
Total (95% CI)	**248**	**241**		**100.0 %**	**0.72 [0.41, 1.25]**
Total events: 21 (Nutrient-enriched formula), 27 (Standard formula)					
Heterogeneity: $Chi^2 = 2.44$, df = 2 (P = 0.30); I^2 =18%					
Test for overall effect: Z = 1.17 (P = 0.24)					
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.85), I^2 =0.0%					



Analysis 1.24. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 24 Duration of birth hospitalisation.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

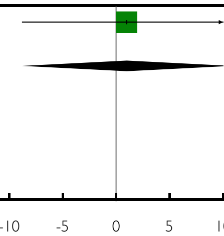
Outcome: 24 Duration of birth hospitalisation

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kulkarni 1984	13	52 (10.8)	18	51 (17)		100.0 %	1.00 [-8.81, 10.81]
Total (95% CI)	**13**		**18**			**100.0 %**	**1.00 [-8.81, 10.81]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable



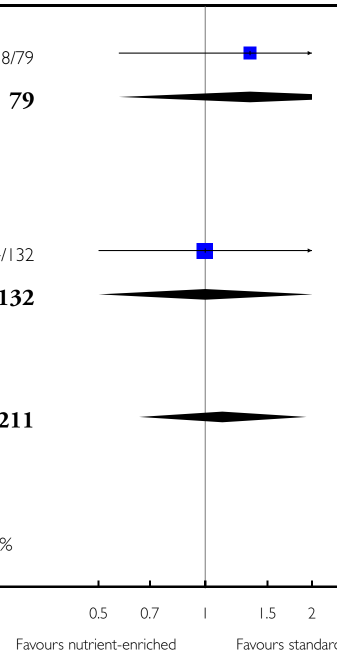
Analysis 1.25. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 25 All-cause mortality.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 25 All-cause mortality

Study or subgroup	Nutrient-enriched formula n/N	Standard formula n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Sole diet					
Lucas 1989a	11/81	8/79		40.1 %	1.34 [0.57, 3.16]
Subtotal (95% CI)	**81**	**79**		**40.1 %**	**1.34 [0.57, 3.16]**
Total events: 11 (Nutrient-enriched formula), 8 (Standard formula)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
2 Supplemental to human milk					
Lucas 1989b	14/132	14/132		59.9 %	1.00 [0.50, 2.01]
Subtotal (95% CI)	**132**	**132**		**59.9 %**	**1.00 [0.50, 2.01]**
Total events: 14 (Nutrient-enriched formula), 14 (Standard formula)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**213**	**211**		**100.0 %**	**1.12 [0.65, 1.93]**
Total events: 25 (Nutrient-enriched formula), 22 (Standard formula)					
Heterogeneity: Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Chi^2 = 0.27, df = 1 (P = 0.60), I^2 =0.0%					



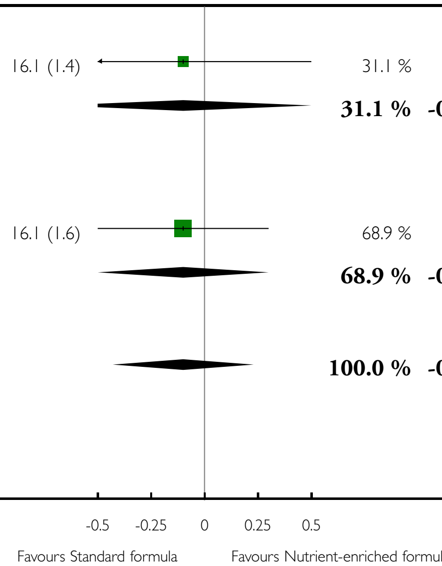
Analysis 1.26. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 26 Body mass index (kg/m²) at 18 months post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 26 Body mass index (kg/m^2) at 18 months post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	61	16 (1.9)	58	16.1 (1.4)		31.1 %	-0.10 [-0.70, 0.50]
Subtotal (95% CI)	**61**		**58**			**31.1 %**	**-0.10 [-0.70, 0.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.33 (P = 0.74)							
2 Supplemental to human milk							
Lucas 1989b	105	16 (1.4)	110	16.1 (1.6)		68.9 %	-0.10 [-0.50, 0.30]
Subtotal (95% CI)	**105**		**110**			**68.9 %**	**-0.10 [-0.50, 0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.63)							
Total (95% CI)	**166**		**168**			**100.0 %**	**-0.10 [-0.43, 0.23]**
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 0.59 (P = 0.56)							
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%							



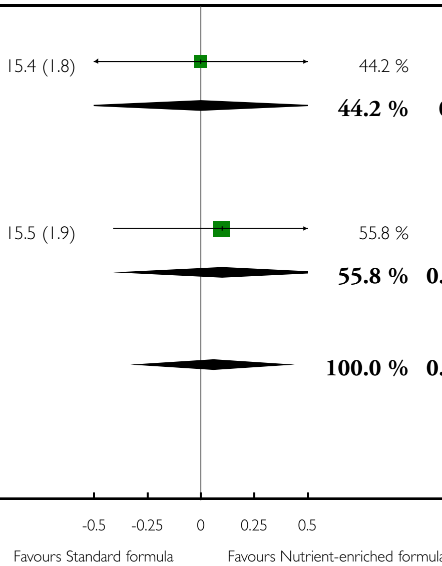
Analysis 1.27. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 27 Body mass index (kg/m²) at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 27 Body mass index (kg/m^2) at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	67	15.4 (1.6)	68	15.4 (1.8)		44.2 %	0.0 [-0.57, 0.57]
Subtotal (95% CI)	**67**		**68**			**44.2 %**	**0.0 [-0.57, 0.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 Supplemental to human milk							
Lucas 1989b	111	15.6 (2)	113	15.5 (1.9)		55.8 %	0.10 [-0.41, 0.61]
Subtotal (95% CI)	**111**		**113**			**55.8 %**	**0.10 [-0.41, 0.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.38 (P = 0.70)							
Total (95% CI)	**178**		**181**			**100.0 %**	**0.06 [-0.33, 0.44]**
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 0.29 (P = 0.77)							
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.80), I^2 =0.0%							



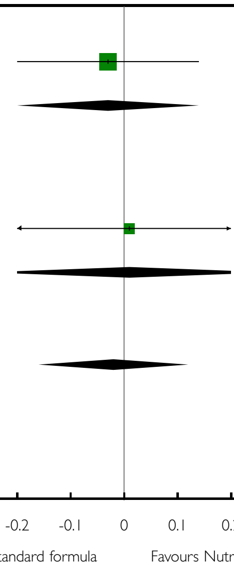
Analysis 1.28. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 28 Waist-to-hip ratio at 7.5 to 8 years post term.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 28 Waist-to-hip ratio at 7.5 to 8 years post term

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sole diet							
Lucas 1989a	67	0.86 (0.41)	68	0.89 (0.58)		71.3 %	-0.03 [-0.20, 0.14]
Subtotal (95% CI)	**67**		**68**			**71.3 %**	**-0.03 [-0.20, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.35 (P = 0.73)							
2 Supplemental to human milk							
Lucas 1989b	111	0.88 (1.37)	113	0.87 (0.43)		28.7 %	0.01 [-0.26, 0.28]
Subtotal (95% CI)	**111**		**113**			**28.7 %**	**0.01 [-0.26, 0.28]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.07 (P = 0.94)							
Total (95% CI)	**178**		**181**			**100.0 %**	**-0.02 [-0.16, 0.12]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² =0.0%							
Test for overall effect: Z = 0.25 (P = 0.80)							
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² =0.0%							



Analysis 1.29. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 29 Serum alkaline phosphatase level after 4 weeks (IU/mL).

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

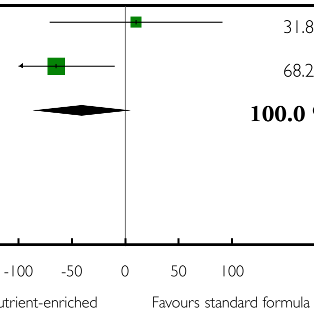
Outcome: 29 Serum alkaline phosphatase level after 4 weeks (IU/mL)

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kashyap 1986	9	287 (107)	9	277 (63)		31.8 %	10.00 [-71.12, 91.12]
Kulkarni 1984	13	305 (72)	18	370 (85)		68.2 %	-65.00 [-120.44, -9.56]
Total (95% CI)	**22**		**27**			**100.0 %**	**-41.12 [-86.89, 4.65]**

Heterogeneity: $Chi^2 = 2.24$, df = 1 (P = 0.13); $I^2 = 55\%$

Test for overall effect: Z = 1.76 (P = 0.078)

Test for subgroup differences: Not applicable



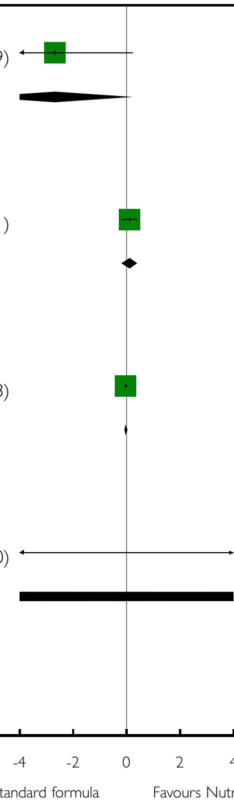
Analysis 1.30. Comparison 1 Nutrient-enriched formula vs standard formula, Outcome 30 Bone mineral content (g) assessed by DEXA at 8 to 12 years.

Review: Nutrient-enriched formula versus standard formula for preterm infants

Comparison: 1 Nutrient-enriched formula vs standard formula

Outcome: 30 Bone mineral content (g) assessed by DEXA at 8 to 12 years

Study or subgroup	Nutrient-enriched formula N	Mean(SD)	Standard formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Lumbar spine							
Lucas 1989a	25	24 (3.5)	36	26.7 (7.9)		100.0 %	-2.70 [-5.62, 0.22]
Subtotal (95% CI)	**25**		**36**			**100.0 %**	**-2.70 [-5.62, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.81 (P = 0.070)							
2 Femoral neck							
Lucas 1989a	25	3.3 (0.55)	36	3.2 (0.61)		100.0 %	0.10 [-0.19, 0.39]
Subtotal (95% CI)	**25**		**36**			**100.0 %**	**0.10 [-0.19, 0.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
3 Radius							
Lucas 1989a	24	0.47 (0.09)	33	0.5 (0.08)		100.0 %	-0.03 [-0.08, 0.02]
Subtotal (95% CI)	**24**		**33**			**100.0 %**	**-0.03 [-0.08, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							
4 Whole body							
Lucas 1989a	24	1061 (1732)	36	1138 (310)		100.0 %	-77.00 [-777.29, 623.29]
Subtotal (95% CI)	**24**		**36**			**100.0 %**	**-77.00 [-777.29, 623.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.22 (P = 0.83)							
Test for subgroup differences: $Chi^2 = 3.99$, df = 3 (P = 0.26), $I^2 = 25\%$							



APPENDICES

Appendix 1. Electronic search strategy

MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily
Ovid SP http://ovidsp.ovid.com/
1946 to November 09, 2018
Searched on: 12^{th} November 2018
Records retrieved: 1621
The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (sensitivity-maximizing version) was used to limit retrieval to clinical trials (lines 23-32) (Lefebvre 2011).
1 exp Infant, Premature/ (51379)
2 exp Infant, Low Birth Weight/ (31813)
3 Premature Birth/ (11445)
4 (preterm or preterms or pre term or pre terms).ti,ab. (66255)
5 (preemie$ or premie or premies).ti,ab. (152)
6 prematur$.ti,ab. (132614)
7 (low adj3 (birthweight$ or birth weight$)).ti,ab. (31857)
8 (lbw or vlbw or elbw).ti,ab. (7551)
9 or/1-8 (220728)
10 Infant Formula/ (3966)
11 formula$.ti,ab. (279507)
12 artificial milk.ti,ab. (205)
13 or/10-12 (280600)
14 Nutriprem.ti,ab. (3)
15 Enfamil premature.ti,ab. (5)
16 Similac special care.ti,ab. (25)
17 Aptamil preterm.ti,ab. (0)
18 Good Start premature.ti,ab. (0)
19 Preemie SMA.ti,ab. (4)
20 or/14-19 (34)
21 13 or 20 (280603)
22 9 and 21 (4416)
23 randomized controlled trial.pt. (471154)
24 controlled clinical trial.pt. (92744)
25 randomized.ab. (426145)
26 placebo.ab. (193103)
27 drug therapy.fs. (2061284)
28 randomly.ab. (300071)
29 trial.ab. (444246)
30 groups.ab. (1850065)
31 or/23-30 (4315602)
32 exp animals/ not humans/ (4513797)
33 31 not 32 (3730894)
34 22 and 33 (1621)
Key
/ = indexing term (MeSH heading)
exp = exploded MeSH heading
$ = truncation
.ti,ab. = terms in either title or abstract fields
adj3 = terms within three words of each other (any order)
.pt.= terms in the publication type field
.fs.= floating subheading

Cochrane Central Register of Controlled Trials (CENTRAL)
Wiley http://onlinelibrary.wiley.com/
Issue 11 of 12, November 2018
Searched on: 13th November 2018
Records retrieved: 1171
#1 MeSH descriptor: [Infant, Premature] explode all trees 3394
#2 MeSH descriptor: [Infant, Low Birth Weight] explode all trees 2040
#3 MeSH descriptor: [Premature Birth] this term only 1028
#4 (preterm or preterms or pre next term or pre next terms):ti,ab,kw 9992
#5 (preemie* or premie or premies):ti,ab,kw 34
#6 prematur*:ti,ab,kw 17871
#7 (low near/3 (birthweight* or birth next weight*)):ti,ab,kw 4419
#8 (lbw or vlbw or elbw):ti,ab,kw 1359
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 23148
#10 MeSH descriptor: [Infant Formula] this term only 532
#11 formula*:ti,ab,kw 30550
#12 artificial milk:ti,ab,kw 585
#13 {OR #10-#12} 30669
#14 Nutriprem:ti,ab,kw 0
#15 Enfamil next premature:ti,ab,kw 1
#16 Similac next special next care:ti,ab,kw 16
#17 Aptamil next preterm:ti,ab,kw 0
#18 Good next Start next premature:ti,ab,kw 0
#19 Preemie next SMA:ti,ab,kw 2
#20 {OR #14-#19} 19
#21 #13 OR #20 30669
#22 #9 AND #21 1287
#23 #9 AND #21 in Trials 1171
Line #23 shows the number of hits in CENTRAL only.
Key
MeSH descriptor = indexing term (MeSH heading)
* = truncation
:ti,ab,kw = terms in either title, abstract or keyword fields
near/3 = terms within three words of each other (any order)
next = terms are next to each other
Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus)
via EBSCO http://www.ebsco.com/
Inception to 12th November 2018
Searched on: 12th November 2018
Records retrieved: 1331
S1 (MH “Infant, Premature”) 19,011
S2 (MH “Infant, Low Birth Weight+”) 11,670
S3 TI (preterm or preterms or pre-term or pre-terms) OR AB (preterm or preterms or pre-term or pre-terms) 25,267
S4 TI (preemie* or premie or premies) OR AB (preemie* or premie or premies) 257
S5 TI prematur* OR AB prematur* 24,035
S6 TI (low N3 (birthweight* or birth-weight*)) OR AB (low N3 (birthweight* or birth-weight*)) 9,594
S7 TI (lbw or vlbw or elbw) OR AB (lbw or vlbw or elbw) 2,590
S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 58,200
S9 (MH “Infant Formula”) 3,551
S10 TI formula* OR AB formula* 37,184
S11 TI artificial milk OR AB artificial milk 91
S12 S9 OR S10 OR S11 38,940
S13 TI Nutriprem OR AB Nutriprem 0

S14 TI Enfamil premature OR AB Enfamil premature 1
S15 TI Similac special care OR AB Similac special care 2
S16 TI Aptamil preterm OR AB Aptamil preterm 0
S17 TI Good Start premature OR AB Good Start premature 1
S18 TI Preemie SMA OR AB Preemie SMA 0
S19 S13 OR S14 OR S15 OR S16 OR S17 OR S18 4
S20 S12 OR S19 38,942
S21 S8 AND S20 1,369
S22 TI rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or sheep or lamb or lambs or pig or pigs or baboon* 65,296
S23 S21 NOT S22 1,331

Key

MH = indexing term (CINAHL heading)
+ = exploded CINAHL heading
* = truncation
TI = words in the title
AB = words in the abstract
N3 = terms within three words of each other (any order)

Embase

Ovid SP http://ovidsp.ovid.com/
1974 to 2018 November 09
Searched on: 12^{th} November 2018
Records retrieved: 1937
The Cochrane EMBASE search strategy for identifying trials for populating CENTRAL (https://www.cochranelibrary.com/central/central-creation) was used as a basis to limit retrieval to clinical trials (lines 22-42).

1 prematurity/ (90414)
2 exp low birth weight/ (55443)
3 (preterm or preterms or pre term or pre terms).ti,ab. (91844)
4 (preemie$ or premie or premies).ti,ab. (227)
5 prematur$.ti,ab. (170179)
6 (low adj3 (birthweight$ or birth weight$)).ti,ab. (39584)
7 (lbw or vlbw or elbw).ti,ab. (10182)
8 or/1-7 (292071)
9 artificial milk/ (12653)
10 formula$.ti,ab. (349334)
11 artificial milk.ti,ab. (229)
12 or/9-11 (353323)
13 Nutriprem.ti,ab. (5)
14 Enfamil premature.ti,ab. (5)
15 Similac special care.ti,ab. (29)
16 Aptamil preterm.ti,ab. (0)
17 Good Start premature.ti,ab. (0)
18 Preemie SMA.ti,ab. (4)
19 or/13-18 (40)
20 12 or 19 (353325)
21 8 and 20 (6391)
22 randomized controlled trial/ (522152)
23 controlled clinical trial/ (458440)
24 Random$.ti,ab. (1348777)
25 randomization/ (80039)
26 intermethod comparison/ (241195)
27 placebo.ti,ab. (278696)
28 (compare or compared or comparison).ti. (463938)

29 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (1821129)
30 (open adj label).ti,ab. (67066)
31 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (211971)
32 double blind procedure/ (155043)
33 parallel group$1.ti,ab. (22476)
34 (crossover or cross over).ti,ab. (94851)
35 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (291657)
36 (assigned or allocated).ti,ab. (342490)
37 (controlled adj7 (study or design or trial)).ti,ab. (304046)
38 (volunteer or volunteers).ti,ab. (227887)
39 human experiment/ (422751)
40 trial.ti. (255652)
41 22 or 23 or 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 or 38 or 39 or 40 (4418563)
42 (animal/ or nonhuman/) not exp human/ (5251547)
43 41 not 42 (3905510)
44 21 and 43 (1937)

Key:

/ = indexing term (EMTREE heading)
exp = exploded EMTREE heading
$ = truncation
$1 = limited truncation - 1 character on none after word stem.
.ti,ab. = terms in either title or abstract fields
adj3 = terms within three words of each other (any order)

Maternity and Infant Care

Ovid SP http://ovidsp.ovid.com/
1971 to September 2018
Searched on: 12 November 2018
Records retrieved: 1060
1 (preterm or preterms or pre term or pre terms).mp. (24959)
2 (preemie$ or premie or premies).mp. (52)
3 prematur$.mp. (22204)
4 (low adj3 (birthweight$ or birth weight$)).mp. (11426)
5 (lbw or vlbw or elbw).mp. (2918)
6 or/1-5 (40035)
7 formula$.mp. (6140)
8 artificial milk.mp. (50)
9 7 or 8 (6180)
10 Nutriprem.mp. (3)
11 Enfamil premature.mp. (1)
12 Similac special care.mp. (6)
13 Aptamil preterm.mp. (0)
14 Good Start premature.mp. (0)
15 Preemie SMA.mp. (0)
16 10 or 11 or 12 or 13 or 14 or 15 (9)
17 9 or 16 (6181)
18 6 and 17 (1060)

Key

$ = truncation
.mp. = multi-purpose field search - includes terms in either title, abstract, keyword heading, name of substance, original title or subject heading fields
adj3 = terms within three words of each other (any order)

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/
Searched on: 12 November 2018
Records retrieved: 63
The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in PubMed (sensitivity-maximizing version) was used to limit retrieval to clinical trials (Lefebvre 2011). The search was limited to those records found in PubMed but not Medline (Duffy 2016).
Search ((((((((((“Infant Formula”[Mesh:NoExp]) OR formula*[Title/Abstract]) OR artificial milk[Title/Abstract])) OR ((((((Nutriprem[Title/Abstract]) OR Enfamil premature[Title/Abstract]) OR Similac special care[Title/Abstract]) OR Aptamil preterm[Title/Abstract]) OR Good Start premature[Title/Abstract]) OR Preemie SMA[Title/Abstract]))) AND ((((((((“Infant, Premature”[Mesh]) OR “Infant, Low Birth Weight”[Mesh]) OR “Premature Birth”[Mesh:NoExp]) OR ((preterm[Title/Abstract] OR preterms[Title/Abstract] OR “pre term”[Title/Abstract] OR “pre terms”[Title/Abstract]))) OR ((preemie*[Title/Abstract] OR premie[Title/Abstract] OR premies[Title/Abstract]))) OR prematur*[Title/Abstract]) OR ((low[Title/Abstract]) AND (birthweight*[Title/Abstract] OR birth-weight*[Title/Abstract]))) OR ((lbw[Title/Abstract] OR vlbw[Title/Abstract] OR elbw[Title/Abstract]))))) AND ((((((((((randomized controlled trial[Publication Type])) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract]))) NOT (animals[mh] NOT humans[mh]))))) AND ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))

Appendix 2. ‘Risk of bias’ tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?
For each included study, we will categorise the method used to generate the allocation sequence as follows.

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

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?
For each included study, we will categorise the method used to conceal the allocation sequence as follows.

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

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?
For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as follows.

- Low risk, high risk, or unclear risk for participants.
- Low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?
For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as follows.

- Low risk for outcome assessors.
- High risk for outcome assessors.
- Unclear risk for outcome assessors.

5. 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 will describe the completeness of data including attrition and exclusions from the analysis. We will note 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 will re-include missing data in the analyses. We will categorise the methods as follows.

- Low risk (< 20% missing data).
- High risk (≥ 20% missing data).
- Unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as follows.

- Low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported).
- High risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and 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 risk.

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

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

- Low risk.
- High risk.
- Unclear risk.

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

Appendix 3. GRADE

The GRADE approach generates an assessment of the certainty of a body of evidence to one of four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- 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.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- 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.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 7, 2019

Date	Event	Description
20 March 2019	Amended	Protocol rewritten by new review author team to update and supersede Simmer 2003

CONTRIBUTIONS OF AUTHORS

All review authors contributed to study selection, data extraction and analysis, and writing of the review. All review authors approved the final review version.

DECLARATIONS OF INTEREST

NDE has conducted research with support from manufacturers of infant formula including Nestec SA (Switzerland), Wyeth UK, and Nutricia UK, but did not receive any payment, support, or benefit in kind for contributions to this review.

VW has no conflicts of interest.

JB has no conflicts of interest.

LA has no conflicts of interest.

WM has no conflicts of interest.

Core editorial and administrative support for this review has been provided by a grant from The Gerber Foundation. The Gerber Foundation is a separately endowed, private foundation, distinct from the Gerber Products Company. The grantor has no input on the content of the review nor on the editorial process.

To maintain the utmost editorial independence for this Cochrane Review, an editor outside of the Cochrane Neonatal core editorial team who is not receiving any financial remuneration from the grant, Eugene Dempsey, was the Sign-off Editor for this review. Additionally, a Senior Editor from the Cochrane Children and Families Network, Robert Boyle, assessed and signed off on this Cochrane Review.

SOURCES OF SUPPORT

Internal sources

- Centre for Reviews and Dissemination, University of York, UK.
- Royal Victoria Infirmary, Newcastle upon Tyne, UK.
- University of Sydney, NWS, Australia.

External sources

- Vermont Oxford Network, USA.

Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

- National Institute for Health Research (NIHR), UK.

This report is independent research funded by a UK NIHR Cochrane Programme Grant (16/114/03). The views expressed in this publication are those of the review authors and are not necessarily those of the National Health Service, the NIHR, or the UK Department of Health.

- The Gerber Foundation, USA.

Editorial support for this review, as part of a suite of preterm nutrition reviews, has been provided by a grant from The Gerber Foundation. The Gerber Foundation is a separately endowed, private, 501(c)(3) foundation not related to Gerber Products Company in any way.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Mortality until 18 months included.