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Young L, Embleton ND, McGuire W

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Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD004696.

DOI: [10.1002/14651858.CD004696.pub5](https://doi.org/10.1002/14651858.CD004696.pub5).

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

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[Intervention Review]

Nutrient-enriched formula versus standard formula for preterm infants following hospital discharge

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Editorial group: Cochrane Neonatal Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2016.

Citation: Young L, Embleton ND, McGuire W. Nutrient-enriched formula versus standard formula for preterm infants following hospital discharge. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD004696. DOI: [10.1002/14651858.CD004696.pub5](https://doi.org/10.1002/14651858.CD004696.pub5).

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ABSTRACT

Background

Preterm infants are often growth-restricted at hospital discharge. Feeding nutrient-enriched formula rather than standard formula to infants after hospital discharge might facilitate 'catch-up' growth and might improve development.

Objectives

To compare the effects of nutrient-enriched formula versus standard formula on growth and development of preterm infants after hospital discharge.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. This included searches of the Cochrane Central Register of Controlled Trials (2016, Issue 8) in the Cochrane Library, MEDLINE, Embase and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; to 8 September 2016), as well as conference proceedings and previous reviews.

Selection criteria

Randomised and quasi-randomised controlled trials that compared the effects of feeding nutrient-enriched formula (postdischarge formula or preterm formula) versus standard term formula to preterm infants after hospital discharge.

Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and extracted data independently. We analysed treatment effects as described in the individual trials and reported risk ratios and risk differences for dichotomous data, and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs). We used a fixed-effect model in meta-analyses and explored potential causes of heterogeneity by performing sensitivity analyses. We assessed quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We included 16 eligible trials with a total of 1251 infant participants. Trials were of variable methodological quality, with lack of allocation concealment and incomplete follow-up identified as major potential sources of bias. Trials (N = 11) that compared feeding infants with 'postdischarge formula' (energy density about 74 kcal/100 mL) versus standard term formula (about 67 kcal/100 mL) did not find consistent evidence of effects on growth parameters up to 12 to 18 months post term. GRADE assessments indicated that evidence was of moderate quality, and that inconsistency within pooled estimates was the main quality issue.

Trials (N = 5) that compared feeding with 'preterm formula' (about 80 kcal/100 mL) versus term formula found evidence of higher rates of growth throughout infancy (weighted mean differences at 12 to 18 months post term: about 500 g in weight, 5 to 10 mm in length, 5 mm in head circumference). GRADE assessments indicated that evidence was of moderate quality, and that imprecision of estimates was the main quality issue.

Few trials assessed neurodevelopmental outcomes, and these trials did not detect differences in developmental indices at 18 months post term. Data on growth or development through later childhood have not been provided.

Authors' conclusions

Recommendations to prescribe 'postdischarge formula' for preterm infants after hospital discharge are not supported by available evidence. Limited evidence suggests that feeding 'preterm formula' (which is generally available only for in-hospital use) to preterm infants after hospital discharge may increase growth rates up to 18 months post term.

PLAIN LANGUAGE SUMMARY

Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge

Review question: Does feeding preterm infants formula enriched with extra nutrients versus standard formula (designed for term infants) after hospital discharge increase growth rate and improve development?

Background: By the time preterm infants are ready to go home from the hospital after receiving care since birth, many are smaller and weigh less than they would have had they stayed in the womb instead of being born early. It may be that feeding preterm infants a formula enriched with extra nutrients (rather than standard formula used to feed term infants) helps them grow more quickly (and catch up with infants born at term) while improving their development.

Study characteristics: We identified 16 eligible trials enrolling a total of 1251 infants through searches updated to 8 September 2016.

Key findings: These trials provide moderate-quality evidence that unrestricted feeding with nutrient-enriched (vs standard) formula does not have important effects on growth and development up to about 18 months of age. Long-term growth and development have not yet been assessed.

Conclusions: Current recommendations to prescribe nutrient-enriched formula for preterm infants after hospital discharge are not supported by available evidence.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Postdischarge formula compared with standard term formula for preterm infants after hospital discharge

Postdischarge formula compared with standard term formula for preterm infants after hospital discharge

Patient or population: preterm infants after hospital discharge

Setting: community

Intervention: postdischarge formula

Comparison: standard term formula

Outcomes	Anticipated absolute effects* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Postdischarge formula vs standard term formula			
Weight (grams) 3-4 months post term	MD 7.45 g lower (141.84 lower to 126.93 higher)	523 (6 RCTs)	⊕⊕⊕⊕ Moderate	Downgraded for moderate inconsistency ($I^2 = 62\%$)
Weight (grams) 6 months post term	MD 35.54 g higher (113.71 lower to 184.78 higher)	576 (7 studies)	⊕⊕⊕⊕ Moderate	Downgraded for inconsistency moderate ($I^2 = 64\%$).
Crown-heel length (mm) 3-4 months post term	MD 2.45 mm higher (2.01 lower to 6.9 higher)	523 (6 RCTs)	⊕⊕⊕⊕ Moderate	Downgraded for high inconsistency ($I^2 = 81\%$)
Crown-heel length (mm) 6 months post term	MD 2.12 mm higher (2.16 lower to 6.41 higher)	576 (7 studies)	⊕⊕⊕⊕ Moderate	Downgraded for moderate inconsistency ($I^2 = 75\%$)
Head circumference (mm) 3-4 months post term	MD 0.3 mm lower (2.86 lower to 2.26 higher)	523 (6 studies)	⊕⊕⊕⊕ Moderate	Downgraded for moderate inconsistency ($I^2 = 71\%$)
Head circumference (mm) 6 months post term	MD 2.28 mm higher (0.28 lower to 4.83 higher)	576 (7 studies)	⊕⊕⊕⊕ Moderate	Downgraded for moderate inconsistency ($I^2 = 69\%$)
Development - Bayley Scales of Infant Development II: Mental Development Index	MD 0.9 higher (3.24 lower to 5.04 higher)	184 (1 RCT)	⊕⊕⊕⊕ High	

Summary of findings 2. Preterm formula compared with standard term formula for preterm infants after hospital discharge

Preterm formula compared with standard term formula for preterm infants after hospital discharge

Patient or population: preterm infants after hospital discharge

Setting: community

Intervention: preterm formula

Comparison: standard term formula

Outcomes	Anticipated absolute effects* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Preterm formula vs standard term formula			
Weight (grams) 3-4 months post term	MD 74.41 g higher (267.1 lower to 415.93 higher)	130 (3 RCTs)	⊕⊕⊕⊖ Moderate	Downgraded for imprecision
Weight (grams) 6 months post term	MD 74.6 g higher (164.73 lower to 313.92 higher)	273 (4 RCTs)	⊕⊕⊕⊖ Moderate	Downgraded for imprecision
Crown-heel length (mm) 3-4 months post term	MD 2.27 mm lower (13.09 lower to 8.56 higher)	130 (3 RCTs)	⊕⊕⊕⊖ Moderate	Downgraded for imprecision
Crown-heel length (mm) 6 months post term	MD 1.83 mm higher (6.25 lower to 9.92 higher)	160 (3 RCTs)	⊕⊕⊕⊖ Moderate	Downgraded for imprecision
Head circumference (mm) 3-4 months post term	MD 3.61 mm higher (2.09 lower to 9.31 higher)	130 (3 RCTs)	⊕⊕⊕⊖ Moderate	Downgraded for imprecision
Head circumference (mm) 6 months post term	MD 5.82 mm higher (1.32 higher to 10.32 higher)	160 (3 RCTs)	⊕⊕⊕⊖ Moderate	Downgraded for imprecision
Development - Bayley Scales of Infant Development II: Mental Development Index	MD 1.44 lower (6.22 lower to 3.35 higher)	143 (2 RCTs)	⊕⊕⊕⊕ High	

BACKGROUND

Compared with term infants, preterm infants have limited nutrient reserves at birth. Also, preterm infants, especially very preterm and very low birth weight (VLBW) infants, are subject to a variety of physiological and metabolic stresses that increase their nutrient needs. Recommended nutrient requirements for preterm infants are based on intrauterine growth studies and assume that the optimal rate of postnatal growth should be about the same as that of uncompromised fetuses of an equivalent postmenstrual age. Evidence indicates, however, that recommended target levels of nutrient input are rarely achieved in practice, and that most very preterm or VLBW infants accumulate significant energy, protein, mineral and other nutrient deficits during their initial hospital stay (Embleton 2001). By the time they are ready to go home, typically at around 36 to 40 weeks' postmenstrual age, many infants are substantially growth-restricted relative to their term-born peers (Clark 2003; Dusick 2003; Lucas 1984).

Description of the condition

After hospital discharge, responsively (demand) fed preterm infants often consume relatively more milk than term infants to attain 'catch-up' growth (Lucas 1992a). Despite this, growth deficits can persist through childhood and adolescence (Bracewell 2008; Farooqi 2006; Ford 2000; Trebar 2007). Slow or incomplete catch-up growth is associated with higher risk of neurodevelopmental impairment in later childhood, and with poorer cognitive and educational outcomes (Cooke 2003; Hack 1991; Leppanen 2014). Preterm infants who have accumulated mineral deficits have higher risks of metabolic bone disease and slower skeletal growth compared with infants born at term, although uncertainty remains about long-term effects of such deficits on bone mass and health (Fewtrell 2011). Furthermore, nutritional deficiency and growth restriction in utero and during early infancy may have consequences for long-term metabolic and cardiovascular health (Embleton 2013; Lapillonne 2013).

Description of the intervention

Because slow or incomplete catch-up growth is associated with prolonged growth restriction and slower neurodevelopmental progression, attention has focused on nutritional interventions that might promote growth during the putative 'critical window' of early infancy in the post-hospital discharge period. Two broad strategies for nutritional interventions are known (Dusick 2003; Fewtrell 2003; Klingenberg 2011).

- Multi-nutrient fortification of expressed milk for infants fed with human breast milk.
- Nutrient-enriched formula for formula-fed infants.

Another Cochrane review addresses the question of whether multi-nutrient fortification of human breast milk affects growth and development in preterm infants after hospital discharge (McCormick 2013). This review focuses on the comparison of nutrient-enriched formula versus standard formula for formula-fed preterm infants after hospital discharge.

A variety of standard and nutrient-enriched formula preparations are available (Aggett 2006; Griffin 2007). These can be categorised broadly as:

- standard term formula: designed for term infants, based on the composition of mature human breast milk. The typical energy content is 66 to 68 kcal/100 mL. The concentration of protein - approximately 1.4 to 1.7 g/100 mL - and calcium and phosphate content (about 50 mg/100 mL and 30 mg/100 mL, respectively) are not sufficient to satisfy recommended nutrient needs for stable and growing preterm infants;
- postdischarge formula: specifically designed for preterm infants post discharge from the hospital. These are energy (about 72 to 74 kcal/100 mL) and protein (about 1.8 to 1.9 g/100 mL) enriched and are variably enriched with minerals, vitamins and trace elements compared with standard term formula. Expert bodies and authorities recommend these formulas for preterm infants for three to 12 months post discharge (Aggett 2006); and
- preterm formula: energy-enriched (about 80 kcal/100 mL), protein-enriched (2.0 to 2.4 g/100 mL) and variably enriched with minerals, vitamins and trace elements to support intrauterine nutrient accretion rates. These formulas are commonly used for nutrition of preterm infants before hospital discharge and generally are not recommended for postdischarge feeding.

How the intervention might work

Feeding preterm infants after hospital discharge formula enriched with extra energy, protein, minerals and vitamins may be expected to promote rapid catch-up growth. However, because preterm infants fed in response to hunger and satiation cues (demand or responsive feeding) adjust their volume of intake according to the energy density of formula, infants may consume less nutrient-enriched milk than standard formula (Lucas 1992a). Consequently, infants fed responsively with preterm or postdischarge formula may not receive any more energy (or other nutrients, depending on the nutrient:energy ratio) than infants fed standard term formula.

Feeding of nutrient-enriched formula may be associated with disordered gastric motility and emptying (Hancock 1984; Siegel 1984). Nutrient-enriched formula may therefore be poorly tolerated, thereby reducing nutrient delivery and potentially removing any benefit for growth and development. Furthermore, catch-up growth with accelerated weight gain and crossing of body mass index (BMI) percentiles might be associated with altered fat distribution and related 'programmed' metabolic consequences that may increase the risk of insulin resistance and cardiovascular disease (Doyle 2004; Euser 2005; Euser 2008; Hack 2003; Saigal 2006).

Why it is important to do this review

Given the potential for postdischarge nutrition strategies to affect growth and development in preterm infants, and the fact that uncertainty surrounds the balance between putative benefits and harms, this review was undertaken to detect, appraise and synthesise available evidence from randomised controlled trials to inform practice and research.

OBJECTIVES

To compare the effects of nutrient-enriched formula versus standard formula on growth and development of preterm infants after hospital discharge.

METHODS

Criteria for considering studies for this review

Types of studies

We included controlled trials using random or quasi-random patient allocation, including cluster-randomised controlled trials. We did not include cross-over trials. Studies published as abstracts were eligible for inclusion only if assessment of study quality was possible, and if other criteria for inclusion were fulfilled.

Types of participants

We included preterm infants fed formula (exclusively or as a supplement to human breast milk) after discharge from hospital. The intervention may have commenced up to one week before planned discharge from hospital. We did not include in this review trials that randomly assigned infants to nutrient-enriched formula versus standard term formula more than one week before hospital discharge (and then continued the intervention after hospital discharge).

Types of interventions

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

versus

- Postdischarge formula: energy content > 72 kcal/100 mL (but ≤ 75 kcal/100 mL) and protein content > 1.7 g/100 mL; or
- Preterm formula: energy content > 75 kcal/100 mL and protein content > 2.0 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 other than the type of formula. Target levels prescribed for volume of intake and advice or support for demand feeding should have been no different among groups.

Types of outcome measures

Primary outcomes

- Growth: weight, length, head growth, skinfold thickness, BMI and measures of body composition (lean/fat mass) and growth restriction (proportion of infants who remain < 10 th percentile for distribution of weight, length or head circumference in the index population). Long-term growth and growth restriction (proportion of infants who remain below the 10th percentile for distribution of weight, height or head circumference in the index population)
- Development
 - Neurodevelopmental outcomes assessed by validated tools at ≥ 12 months' corrected age; classifications of disability, including non-ambulant cerebral palsy, developmental delay and auditory and visual impairment
 - Cognitive and educational outcomes at ≥ 5 years: intelligence quotient and/or indices of educational achievement measured by a validated tool (including school examination results)

Secondary outcomes

- Feed intolerance such as vomiting or diarrhoea that necessitates ceasing the study formula
- Measures of bone mineralisation such as serum alkaline phosphatase level, or assessment of bone mineral content by dual-energy X-ray absorptiometry and clinical or radiological evidence of rickets on long-term follow-up
- Blood pressure on long-term follow-up
- Body mass index or other measures of overweight or obesity on long-term follow-up

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group.

Electronic searches

We updated the search on 8 September 2016 using a combination of the following terms: (infant nutrition OR infant formula OR milk OR formula OR nutrient OR fortif* OR supplement*) AND (postdischarge OR post-discharge OR discharge) plus the following database-specific terms limited by relevant search filters for clinical trials, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.

- PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
- Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
- Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

We applied no language restrictions.

We searched ClinicalTrials.gov and [Current Controlled Trials](#) for completed and ongoing trials.

Searching other resources

We examined the references provided in studies identified as potentially relevant. We searched abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2016), the European Society for Pediatric Research (1995 to 2016), the UK Royal College of Paediatrics and Child Health (2000 to 2016) and the Perinatal Society of Australia and New Zealand (2000 to 2016). We considered trials reported only as abstracts to be eligible

if sufficient information was available from the report, or from contact with study authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

Two review authors screened the titles and abstracts of all studies identified by the above search strategy. We reassessed the full texts of potentially eligible reports and excluded studies that did not meet all of the inclusion criteria. We discussed disagreements until consensus was achieved.

Data extraction and management

We used a data collection form to aid extraction of relevant information from each included study. Two review authors extracted study data separately. We discussed disagreements until consensus was achieved and asked investigators for further information if data provided in the trial reports were insufficient.

Assessment of risk of bias in included studies

We used criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of included trials. Two review authors conducted assessment of risk of bias and resolved disagreements by discussion. We requested additional information from trial authors to clarify methods and results if necessary.

We made explicit judgements about whether studies were at high risk of bias across four domains, according to the criteria suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- Random sequence generation: We categorised the method used to generate the allocation sequence as:
 - * 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); or
 - * unclear risk - no or unclear information provided.
- Allocation concealment: We categorised the method used to conceal the allocation sequence as:
 - * low risk (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
 - * high risk - open random allocation (e.g. unsealed or non-opaque envelopes, alternation; date of birth); or
 - * unclear - no or unclear information provided.
- Blinding: We assessed blinding of participants, clinicians and caregivers and outcome assessors separately for different outcomes and categorised the methods as:
 - * low risk;
 - * high risk; or
 - * unclear risk.
- Incomplete outcome data: We described completeness of data, including attrition and exclusions from analysis for each outcome and reasons for attrition or exclusion, when reported. We assessed whether missing data were balanced across groups or were related to outcomes. When sufficient information

was reported or was supplied by trial authors, we planned to reinstate missing data to the analyses. We categorised completeness as:

- low risk: $\leq 10\%$ missing data;
- high risk: $> 10\%$ missing data; or
- unclear risk: no or unclear information provided.

We assessed the likely magnitude and direction of bias and whether we considered it likely for bias to impact study findings. We planned to explore the impact of the level of bias by performing sensitivity analyses.

Measures of treatment effect

We analysed treatment effects in individual trials by using Review Manager 5.3 and reported risk ratios (RRs) and risk differences (RDs) for dichotomous data and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with statistically significant differences among RDs.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. For cluster-randomised trials (had we identified any for inclusion), we planned to undertake analyses at the level of the individual while accounting for clustering of data by using methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We requested additional data from trial investigators if data on important outcomes were missing or were reported unclearly. When data were still missing, we examined the impact of this on effect size estimates by performing sensitivity analyses.

Assessment of heterogeneity

We examined treatment effects in individual trials and heterogeneity between trial results by inspecting forest plots if more than one trial was included in a meta-analysis. 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. If we detected moderate or high ($I^2 > 50\%$) heterogeneity, we explored possible causes (e.g. differences in study design, participants or interventions; completeness of outcome assessments) by performing sensitivity analyses.

Assessment of reporting biases

If more than five trials were included in a meta-analysis, we conducted a funnel plot analysis.

Data synthesis

We used the fixed-effect model in RevMan 5.1 to perform meta-analysis.

Quality of evidence

We assessed the quality of evidence for the main comparison at the outcome level by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

(Guyatt 2011a), which considers evidence from randomised controlled trials as of high quality that may be downgraded on the basis of consideration of any of five areas.

- Design (risk of bias).
- Consistency across studies.
- Directness of the evidence.
- Precision of estimates.
- Presence of publication bias.

The GRADE approach is used to assess the quality of a body of evidence according to four grades (Schünemann 2013).

- High: We are very confident that the true effect lies close to the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of 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.

Two review authors assessed independently the quality of the evidence for outcomes identified as critical or important for clinical decision making (growth, development).

In cases for which we considered risk of bias to arise from inadequate concealment of allocation, randomised assignment, complete follow-up or blinded outcome assessment, to reduce our confidence in the effect estimates, we downgraded the quality of evidence accordingly (Guyatt 2011b). We evaluated consistency on the basis of similarity of point estimates, extent of overlap of confidence intervals and statistical criteria, including measurement of heterogeneity (I^2). We downgraded the quality of evidence when

inconsistency across study results was large and unexplained (i.e. some studies suggested important benefit, and others no effect or harm with no explanation) (Guyatt 2011c). We assessed precision accordingly with the 95% confidence interval (CI) around the pooled estimation (Guyatt 2011d). When trials were conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness (Guyatt 2011e).

We entered data (pooled estimates of effects and 95% CIs) and explicit judgements for each of the above aspects assessed into the Guideline Development Tool, the software used to create 'Summary of findings (SoF)' tables (GRADEpro 2008). We explained our assessment of study characteristics in footnotes in the SoF table.

Subgroup analysis and investigation of heterogeneity

We prespecified the following subgroup analyses.

- Very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants (vs infants at 32 to 36 weeks' gestation or birth weight 1500 to 2499 g).
- Infants who were small for gestational age (< 10th percentile for weight) at hospital discharge (vs infants $\geq$ 10th percentile).
- Infants with chronic lung disease receiving supplemental oxygen therapy at hospital discharge (vs infants without chronic lung disease).

RESULTS

Description of studies

We identified two potentially eligible study reports. We included one new trial (Roggero 2011). We have not yet been able to obtain the full article reporting a potentially eligible trial and have categorised this as a 'study awaiting classification' (Ekcharoen 2015). See Figure 1.

Figure 1. Study flow diagram: review update.

Included studies

In total, we identified 16 trials that fulfil review eligibility criteria (Agosti 2003; Atkinson 1999; Atkinson 2004; Carver 2001; Cooke 2001; De Curtis 2002; Jeon 2011; Koo 2006; Litmanovitz 2004; Lucas 1992; Lucas 2001; Peng 2004; Picaud 2005; Roggero 2011; Roggero 2012; Taroni 2009). See [Characteristics of included studies](#).

Participants

Trials were undertaken within the past 20 years by investigators attached to perinatal centres in Europe, North America and the Middle East. In total, 1251 infants participated in these trials (range 20 to 229).

Most trials specified a maximum birth weight as the primary eligibility criterion.

- 1500 g: [Agosti 2003](#); [Litmanovitz 2004](#); [Jeon 2011](#); [Taroni 2009](#).
- 1750 g: [Cooke 2001](#); [De Curtis 2002](#); [Lucas 2001](#); [Picaud 2005](#).
- 1800 g: [Atkinson 1999](#); [Carver 2001](#).
- 1850 g: [Lucas 1992](#); [Peng 2004](#).

Four trials specified gestational age as an eligibility criterion.

- < 35 weeks: [Koo 2006](#).
- < 37 weeks: [Atkinson 2004](#); [Roggero 2011](#); [Roggero 2012](#).

Three trials specifically recruited participants who were small for gestational age.

- Birth weight < 5th percentile: [Atkinson 2004](#).
- Birth weight < 10th percentile: [Taroni 2009](#); [Roggero 2012](#).

Although most reports of the other trials did not specify intrauterine or postnatal growth restriction as an exclusion criterion, it appears that very few participants in the trials were small for gestational age at birth or enrolment. Generally, infants with additional problems at discharge, particularly those with inadequate independent oral feeding or receipt of supplemental oxygen secondary to chronic lung disease, were not eligible to participate.

Interventions

Postdischarge formula versus standard term formula (Comparison 1)

Eleven trials (N = 885): [Atkinson 1999](#); [Atkinson 2004](#); [Carver 2001](#); [De Curtis 2002](#); [Koo 2006](#); [Litmanovitz 2004](#); [Lucas 1992](#); [Lucas 2001](#); [Roggero 2011](#); [Roggero 2012](#); [Taroni 2009](#).

Preterm formula versus standard term formula (Comparison 2)

Five trials (N = 366): [Agosti 2003](#); [Cooke 2001](#); [Jeon 2011](#); [Peng 2004](#); [Picaud 2005](#).

All participating infants were fed ad libitum. These feeds were intended to be the principal source of milk for a range of periods post term (or post hospital discharge).

- One month: [Taroni 2009](#).
- Two months: [De Curtis 2002](#); [Picaud 2005](#).
- Three months: [Agosti 2003](#); [Jeon 2011](#).
- Six months: [Cooke 2001](#); [Litmanovitz 2004](#); [Peng 2004](#); [Roggero 2011](#); [Roggero 2012](#).
- Nine months: [Lucas 1992](#); [Lucas 2001](#).
- Up to 12 months: [Atkinson 1999](#); [Atkinson 2004](#); [Carver 2001](#); [Koo 2006](#).

Outcomes

The main outcomes assessed were growth parameters (weight, length and occipitofrontal head circumference) assessed up to 12 to 18 months' corrected age. Three trials assessed neurodevelopmental outcomes at 18 months using Bayley Scales of Infant Development II ([Cooke 2001](#); [Jeon 2011](#); [Lucas 2001](#)). One trial used Griffiths' Developmental Scales at six, nine and 12 months' corrected age ([Agosti 2003](#)).

Excluded studies

We excluded nine studies ([Amesz 2010](#); [Bernbaum 1989](#); [Bhatia 1991](#); [Brunton 1998](#); [Chan 1994](#); [Cooper 1985](#); [Friel 1993](#); [Lapillonne 2004](#); [Wheeler 1996](#)) and listed reasons for exclusion in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Trials were of variable methodological quality ([Figure 2](#)).

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

Allocation

In eight trials ([Atkinson 1999](#); [Atkinson 2004](#); [Cooke 2001](#); [Koo 2006](#); [Lucas 2001](#); [Picaud 2005](#); [Roggero 2011](#); [Roggero 2012](#)), the method of randomisation described was likely to ensure blinding of allocation. In the other trials, it is not clear whether allocation concealment was adequate. In one of these trials, substantial between-group differences in baseline demographic

characteristics were evident, most likely due to allocation bias ([Jeon 2011](#)). This trial originally randomised participants to one of three intervention groups. We elected to discard data from the group in which infant characteristics were statistically significantly different from those of other groups at enrolment.

Blinding

Most trials blinded families to the type of milk that the infant received. In three trials (Agosti 2003; Jeon 2011; Peng 2004), it is likely that families were aware of which type of milk their infant had been allocated to receive. It is unclear whether blinding was satisfactory in another four trials (Litmanovitz 2004; Roggero 2011; Roggero 2012; Taroni 2009).

Most trials blinded outcome assessors and investigators to the type of milk that the infant received, but in five trials (Jeon 2011; Litmanovitz 2004; Roggero 2011; Roggero 2012; Taroni 2009), it is unclear whether blinding was satisfactory. In one trial (Peng 2004), physicians were unblinded.

Incomplete outcome data

Eleven trials (Atkinson 2004; Cooke 2001; De Curtis 2002; Jeon 2011; Litmanovitz 2004; Lucas 1992; Lucas 2001; Peng 2004; Roggero 2011; Roggero 2012; Taroni 2009) achieved complete or near-complete (> 90%) assessment. In two other trials (Atkinson 1999; Koo 2006), 75% of infants underwent outcome assessments at latest follow-up. In another two trials (Agosti 2003; Carver 2001), less than 50% of infants completed the planned 12-month follow-up assessment. In Picaud 2005, loss to follow-up by 12 months in the control group was substantial (35%) and was greater than in the intervention group (9%).

Effects of interventions

See: [Summary of findings for the main comparison Postdischarge formula compared with standard term formula for preterm infants after hospital discharge](#); [Summary of findings 2 Preterm formula compared with standard term formula for preterm infants after hospital discharge](#)

Postdischarge formula versus standard term formula (Comparison 1)

Growth (Outcomes 1.1 to 1.4)

Lucas 1992 detected no statistically significant differences in weight, length or head circumference at the end of intervention and follow-up periods (nine months' corrected age).

Atkinson 1999 reported that infants who received postdischarge formula were statistically significantly heavier at six, nine and 12 months' corrected age, and researchers noted no statistically significant differences in length or head circumference.

Carver 2001 detected no statistically significant differences in weight, length or head circumference at six and 12 months'

corrected age. Loss to follow-up during the trial was substantial, and as the published report does not state how many infants were assessed at various time points, we could not use data to calculate mean differences.

Lucas 2001 reported that at completion of the intervention period (nine months' corrected age), weight and length were statistically significantly greater among infants who received postdischarge formula but noted no statistically significant differences in head circumference. At 18 months, results showed no statistically significant differences in weight or head circumference. The group of infants who received postdischarge formula remained statistically significantly longer on average than infants in the control group (MD 9.0, 95% CI 0.3 to 17.7 mm).

De Curtis 2002 found no statistically significant differences in rate of gain of weight, length or head circumference during the two-month trial period.

Atkinson 2004 reported no statistically significant differences in rate of gain of weight, length or head circumference up to 12 months' corrected age (growth data reported as z scores).

Litmanovitz 2004 noted no statistically significant differences in weight, length or head circumference at six months' corrected age.

Koo 2006 reported that mean weight, head circumference and length were less in the nutrient-enriched formula group at six, nine and 12 months after hospital discharge.

Taroni 2009 found no statistically significant differences in weight, length or head circumference at one month corrected age.

Roggero 2011 reported no statistically significant differences in weight, length or head circumference at three, six or 12 months' corrected age.

Roggero 2012 noted no statistically significant differences in weight, length or head circumference at three, six or 12 months' corrected age.

Meta-analyses of growth data

- Weight (Outcome 1.2; [Figure 3](#)): Meta-analyses detected no statistically significant differences in weight at three to four and six months' corrected age. At nine months, meta-analysis of data from four trials (Atkinson 1999; Koo 2006; Lucas 1992; Lucas 2001) indicated that infants in the postdischarge formula group were heavier (weighted mean difference (WMD) 244, 95% CI 17 to 471 g). At 12-month follow-up, results showed no statistically significant differences.

Figure 3. Forest plot of comparison: 1 Postdischarge formula versus standard term formula, outcome: 1.2 Weight (grams).

- Length (Outcome 1.3; Figure 4): Meta-analyses detected no statistically significant differences in weight at three to four and six months' corrected age. At nine months, meta-analysis of data from four trials (Atkinson 1999; Koo 2006; Lucas 1992; Lucas

2001) indicated that infants in the postdischarge formula group were longer (WMD 7.3, 95% CI 1.8 to 12.9 mm). At 12-month follow-up, results showed no statistically significant differences.

Figure 4. Forest plot of comparison: 1 Postdischarge formula versus standard term formula, outcome: 1.3 Crown-heel length (mm).

- Head circumference (Outcome 1.4; Figure 5): Meta-analyses detected no statistically significant differences at three to four, six, nine or 12 months.

Figure 5. Forest plot of comparison: 1 Postdischarge formula versus standard term formula, outcome: 1.4 Head circumference (mm).

All meta-analyses showed substantial statistical heterogeneity ($I^2 > 50\%$).

Development (Outcome 1.5)

Lucas 2001 did not detect a statistically significant difference in the Bayley Scales Mental or Psychomotor Development Index at 18 months' corrected age. None of the included trials assessed later cognitive and educational outcomes.

Feed intolerance

Only one trial assessed this outcome (Lucas 1992) and reported no statistically significant difference in the mean number of vomits or possets per day. None of the participating infants ceased taking a study formula because of feed intolerance.

Bone mineralisation (Outcome 1.6)

Atkinson 2004 found no statistically significant differences in bone mineral content assessed at 12 months' corrected age (numerical data not available).

De Curtis 2002 reported no statistically significant differences in bone mineral content nor in bone area at the end of the two-month study period.

Koo 2006 reported that at the end of the 12-month study period, infants who received nutrient-enriched formula had statistically significantly lower bone mass (measured by dual-energy X-ray absorptiometry). Investigators presented data in graphs only, and data could not be extracted or obtained for calculation of mean differences.

Lucas 1992 assessed bone width and bone mineral content of the radius at nine months' corrected age. Bone width was not

statistically significantly different between groups. Bone mineral content was statistically significantly greater in the group of infants who received the postdischarge formula: mean difference 20.6, 95% CI 7.8 to 33.4 mg/cm.

[Litmanovitz 2004](#) found no statistically significant differences in bone strength assessed as 'bone speed of sound' on measurement with ultrasonography, nor in serum levels of bone-specific alkaline phosphatase, at six months' corrected age.

No trials assessed the effect of the intervention on clinical or radiological evidence of rickets.

Blood pressure on long-term follow-up

No included trials performed this assessment.

Body mass index on long-term follow-up

No included trials performed this assessment.

Subgroup analyses

- VLBW or very preterm infants: Two trials ([Litmanovitz 2004](#); [Taroni 2009](#)) recruited exclusively VLBW infants. As described above, investigators found no statistically significant differences in weight, length or head circumference, nor in measures of bone mineralisation, up to six months' corrected age.
- Infants who remain small for gestational age at hospital discharge: Three trials ([Atkinson 2004](#); [Roggero 2012](#); [Taroni 2009](#)) recruited infants who were growth-restricted at birth. These trials detected no statistically significant effects on weight up to 12 months' corrected age, but meta-analyses of data from the two trials that undertook follow-up at six months ([Atkinson 2004](#); [Roggero 2012](#)) revealed statistically significant effects on crown-heel length (WMD 8.88, 95% CI 0.94 to 16.83 mm) and on head circumference (WMD 5.36, 95% CI 0.62 to 10.11 mm).
- Infants with chronic lung disease requiring home supplemental oxygen therapy: No trials exclusively recruited infants with chronic lung disease. Subgroup data were not available.

Preterm formula versus standard term formula (Comparison 2)

Growth (Outcomes 2.1-2.4)

[Cooke 2001](#) found no statistically significant differences in rate of weight gain during the trial period. Researchers presented data

in graphs only, and data could not be extracted or obtained for calculation of the mean difference. At 18 months' corrected age, the nutrient-enriched formula group was statistically significantly heavier than the control group (MD 500, 95% CI 26 to 974 g), but investigators noted no statistically significant differences in length or head circumference.

[Agosti 2003](#) reported no statistically significant differences in mean weight, length or head circumference at four, six and 12 months after hospital discharge.

[Peng 2004](#) noted no statistically significant differences in mean weight, length or head circumference at monthly intervals up to six months' corrected age.

[Picaud 2005](#) observed no statistically significant differences in rate of gain of weight, length or head circumference during the first four months of the trial period and no statistically significant differences in weight, length or head circumference between groups at four months. At 12 months post discharge, infants in the preterm formula group were heavier (MD 1007, 95% CI 211 to 1803 g) (Outcome 2.2), were longer (MD 27, 95% CI 2 to 52 mm) (Outcome 2.3) and had larger head circumference (MD 12, 95% CI 0.2 to 24 mm) (Outcome 2.4) than control infants. However, loss to follow-up by 12 months was substantial in the control group (35%) and was greater than that reported for the intervention group (9%).

[Jeon 2011](#) found no statistically significant differences in mean weight, length or head circumference at three, 12 and 18 months after hospital discharge.

Meta-analyses of growth data

- Weight (Outcome 2.2; [Figure 6](#)): Meta-analysis of data from four trials ([Agosti 2003](#); [Cooke 2001](#); [Jeon 2011](#); [Picaud 2005](#)) showed statistically significantly higher weight in the preterm formula group at 12 months' corrected age (WMD 540, 95% CI 255 to 824 g). Meta-analysis of data from two trials ([Cooke 2001](#); [Jeon 2011](#)) revealed statistically significantly higher weight in the preterm formula group at 18 months (WMD 491, 95% CI 142 to 839 g) (Outcome 2.2).

Figure 6. Forest plot of comparison: 2 Preterm formula versus standard term formula, outcome: 2.2 Weight (grams).

- Length (Outcome 2.3; Figure 7): Meta-analysis of data from three trials (Agosti 2003; Jeon 2011; Picaud 2005) showed no statistically significant difference at 12 months' corrected age (WMD 5.1, 95% CI -4.2 to 14.5 mm). Meta-analysis of data

from two trials (Cooke 2001; Jeon 2011) revealed statistically significantly longer crown-heel length in the preterm formula group at 18 months (WMD 11, 95% CI 2 to 20 mm).

Figure 7. Forest plot of comparison: 2 Preterm formula versus standard term formula, outcome: 2.3 Crown-heel length (mm).

- Head circumference (Outcome 2.4; [Figure 8](#)): Meta-analysis of data from three trials ([Agosti 2003](#); [Jeon 2011](#); [Picaud 2005](#)) showed a statistically significantly larger head circumference in the preterm formula group at 12 months' corrected age (WMD

6.1, 95% CI 1.1 to 11.1 mm). Meta-analysis of data from two trials ([Cooke 2001](#); [Jeon 2011](#)) revealed a statistically significantly larger head circumference in the preterm formula group at 18 months (WMD 5.4, 95% CI 0.7 to 10.1 mm).

Figure 8. Forest plot of comparison: 2 Preterm formula versus standard term formula, outcome: 2.4 Head circumference (mm).

Development (Outcome 2.5)

Neither [Cooke 2001](#) nor [Jeon 2011](#) nor a meta-analysis of data from both trials detected a statistically significant difference in the Bayley Scales Mental Development Index (WMD -1.4, 95% CI -6.2 to 3.4) or in the Psychomotor Development Index (WMD -1.1, 95% CI -4.2 to 1.93). [Agosti 2003](#) noted no statistically significant differences in Griffiths' Developmental Scale evaluations at six, nine and 12 months' corrected age (numerical data not available from report nor from trialists).

Feed intolerance

No included trials performed this assessment.

Bone mineralisation

[Cooke 2001](#) assessed body composition with dual-energy X-ray absorptiometry at six and 12 months' corrected age and noted no statistically significant differences in bone area, bone mineral mass or bone mineral density measurements between groups. In the published report, all data were presented in graphs and could not be extracted for estimation of mean differences. Investigators also reported that they found no statistically significant differences in serum phosphorus, calcium and alkaline phosphatase levels measured at intervals during the study period (up to six months

post term). These data were presented mainly in graphs and could not be extracted for estimation of mean differences.

Blood pressure on long-term follow-up

No included trials performed this assessment.

Body mass index on long-term follow-up

No included trials performed this assessment.

Subgroup analyses

- VLBW or very preterm infants: Two trials ([Agosti 2003](#); [Jeon 2011](#)) exclusively recruited VLBW infants. See details of findings described above. Subgroup data from the other trials were not available.
- Infants who remain small for gestational age at hospital discharge: Subgroup data were not available.
- Infants with chronic lung disease requiring home supplemental oxygen therapy: Subgroup data were not available.

DISCUSSION

Summary of main results

Data from 11 randomised controlled trials with a total of 885 participants provided no evidence that feeding postdischarge formula (~74 kcal/100 mL) versus standard term formula (~67 kcal/100 mL) to preterm infants after hospital discharge affects growth parameters up to 12 to 18 months post term.

The five trials that examined the effect of feeding preterm formula (~80 kcal/100 mL) versus standard term formula provided some evidence of an effect on growth parameters. Meta-analyses showed a weighted mean difference of about 500 g for weight, 11 mm for length and 5 to 6 mm for head circumference at 12 to 18 months post term. It is not yet known whether any of these differences persist through later childhood.

Evidence of the effects of nutrient-enriched formula on long-term development is unclear. The only trial of postdischarge versus term formula conducted to assess developmental outcomes showed no difference in the Bayley Scales Mental or Psychomotor Development Index assessed at 18 months' corrected age ([Lucas 2001](#)). Similarly, meta-analyses of data from two trials provided no evidence that feeding preterm versus term formula affects neurodevelopmental outcomes at 18 months' corrected age. Data on longer-term cognitive and educational outcomes are not yet available.

Overall completeness and applicability of evidence

We identified 11 eligible trials that compared feeding with postdischarge formula versus term formula, but studies generally were small and of variable methodological quality. Quantitative synthesis was limited, as only seven of these trials ([Atkinson 1999](#); [Koo 2006](#); [Litmanovitz 2004](#); [Lucas 1992](#); [Lucas 2001](#); [Roggero 2011](#); [Roggero 2012](#)) presented data that could be included in meta-analyses of growth outcomes. Interpretation of meta-analyses was further limited by heterogeneity. The source of heterogeneity is not clear, as these trials were of similar design (intervention given for six to 12 months) and methodological quality (satisfactory processes to ensure allocation concealment and achievement of about 70% to 80% follow-up at longer than six months post term). Meta-analyses of data from the five trials that compared preterm formula versus term formula were more complete and revealed no statistical heterogeneity.

Differences in measured effects on growth parameters between postdischarge formula and preterm formula may simply be related to total nutrient content and intake. An additional factor is that whereas postdischarge formula contains about 10% more calories and 20% to 25% more protein and bone minerals than term formula, preterm formula is about 20% energy-enriched and contains 40% to 60% more protein and minerals than term formula. Demand (responsively) fed infants regulate their volume of milk intake relative to its calorie density; therefore, infants in comparison groups may have had similar total energy intake. However, infants fed postdischarge formula would still have received about 10% more protein and minerals than those fed term formula, but infants fed preterm formula would have received up to about 25% more protein and minerals than those given term formula. It is possible that protein and mineral intake (per unit of

energy) is the key factor in determining catch-up growth rates and, specifically, lean and skeletal growth, in this population of infants.

The applicability of currently available data is limited by the short duration of follow-up reported in clinical trials. No trials planned to undertake or undertook assessment of growth or development beyond 12 to 18 months' corrected age, and some trials reported growth outcomes only up to six months. Similarly, no trials have reported data related to possible adverse metabolic consequences of nutrient supplementation in early infancy, nor to any long-term measures of obesity (such as body mass index (BMI), fat mass) or risk factors for cardiovascular disease (such as elevated blood pressure).

Quality of the evidence

Interpretation of review findings is limited by methodological weaknesses associated with potential for bias in some trials ([Figure 2](#)). Methods used to preserve allocation concealment are uncertain for some trials. Only one trial ([Jeon 2011](#)) reported substantial between-group differences in baseline demographics that are likely due to allocation bias. We elected to exclude one arm of this three-arm trial because of substantial differences in mean birth weight, gestational age and proportion of growth-restricted infants. The other methodological limitation apparent in six trials was incomplete outcome assessment (loss to follow-up > 20%). In most of these trials ([Atkinson 1999](#); [Koo 2006](#); [Peng 2004](#); [Picaud 2005](#)), loss to follow-up was less than 30% and was distributed evenly between intervention and control groups. In two trials ([Agosti 2003](#); [Carver 2001](#)), loss to follow-up at 12-month assessment was greater than 50%. However, these trials did not contribute substantially to any meta-analyses.

The GRADE assessment revealed that evidence for key growth outcomes was of moderate quality because of inconsistency (moderate or high heterogeneity in meta-analyses of trials of postdischarge formula vs standard formula; [Summary of findings for the main comparison](#)) and imprecision (few trials with low numbers of participants included in meta-analyses of preterm formula vs standard formula; [Summary of findings 2](#)).

Potential biases in the review process

Our main concern with the review process is that findings may be 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 ([Hopewell 2009](#)). We attempted to minimise this threat by searching the proceedings of major international perinatal conferences to identify trial reports that were not (or were not yet) published in full form in academic journals. However, we cannot be sure whether other trials have been undertaken but not reported, and we remain concerned 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 the symmetry of funnel plots as a means of identifying possible publication or reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

These findings do not support expert group and consensus recommendations that formula-fed preterm infants should receive

a postdischarge formula for up to 12 months after discharge from the hospital ([Aggett 2006](#); [Bhatia 2005](#); [Carver 2005](#); [Dusick 2003](#); [Griffin 2007](#); [Kleinman 2004](#)). In contrast, available trial data indicate that feeding with 'preterm formula', which generally is licensed and available only for in-hospital use, may increase weight, length and head circumference growth up to 12 to 18 months post term.

Infants who participated in the trials included in this review were fed responsively (on demand), and study findings may not be applicable to infants who cannot feed responsively, for example, because of oro-motor dysmotility or chronic lung disease.

Implications for research

Follow-up of infants who participated in the trials identified in this review might provide further data on the effect of this intervention on growth through later childhood, specifically, whether final height is affected; on effects on later neurodevelopmental outcomes; and on long-term effects on metabolic or cardiovascular outcomes ([Euser 2005](#); [Greer 2007](#)). If additional large randomised controlled trials are undertaken to evaluate the effects of feeding preterm infants with nutrient-enriched formula after hospital discharge, it may be appropriate to include in these research efforts preterm infants who are not able to feed ad libitum after hospital discharge, and who have extra metabolic demands, for example, because of severe growth restriction or chronic lung disease. Trials

should aim to assess long-term clinically important outcomes such as final height and body composition and neurodevelopment (including cognitive and educational outcomes).

Further research is needed to determine which specific nutrients (including appropriate energy:protein balance) are key to promoting lean mass and linear growth and to improving developmental outcomes. As a first step, it may be worthwhile to review systematically trials that could not be included in this review because the nutrient-enriched formula examined differed only in protein and mineral content (but not in energy) from standard term formula.

ACKNOWLEDGEMENTS

We thank Dr Litmanovitz for clarifying aspects of [Litmanovitz 2004](#).

We thank Dr Roggero for kindly providing unpublished data from [Roggero 2011](#) for inclusion in this review.

We thank Yolanda Brosseau and Colleen Ovelman of the Cochrane Neonatal Review Group for help in preparing this updated review.

Editorial support of the Cochrane Neonatal Review Group has been provided with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agosti 2003

Methods	Randomised controlled trial
Participants	121 formula milk-fed VLBW (< 1500 g) infants
Interventions	Preterm formula (energy content 80 kcal/100 mL, protein content 2.4 g/100 mL, calcium and phosphorus content 100 mg/100 mL and 50 mg/100 mL, respectively) (N = 69) or standard term formula (energy content 70 kcal/100 mL, protein content 1.7 g/100 mL) (N = 52). The intention was for the allocated formula to be the only milk source from 40 weeks until 55 weeks postmenstrual age (PMA)

Agosti 2003 (Continued)

Outcomes	Growth parameters and Griffiths Developmental Scale at 40 weeks, 55 weeks PMA and 6 and 12 months' corrected age
Notes	Setting: multi-centre trial in Italy (2001) Research supported by Milupa (formula milk manufacturing company) Numerical growth data obtained from primary investigators (June 2011)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Report states simply that infants were "randomised" to study groups.
Allocation concealment (selection bias)	Unclear risk	Randomisation method was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up was 34% at 6 months and 66% at 12 months.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Families and caregivers were aware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were unlikely to have been aware of which formula milk infants received.

Atkinson 1999

Methods	Randomised controlled trial
Participants	70 formula milk-fed preterm infants of birth weight < 1800 g and 'appropriate for gestational age'
Interventions	Postdischarge formula (energy content 74 kcal/100 mL, protein content 1.8 g/100 mL) (N = 34) vs standard term formula (N = 36) for 12 months post discharge
Outcomes	Growth parameters at 6, 9 and 12 months' corrected age
Notes	Published in abstract form only. Additional information and data courtesy of Dr Stephanie Atkinson

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was independently generated.
Allocation concealment (selection bias)	Low risk	Allocation was drawn from sequential sealed opaque envelopes.

Atkinson 1999 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Growth outcome data to 12 months were available for 24 (71%) intervention group and 29 (81%) control group infants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of which formula milk infants received.

Atkinson 2004

Methods	Randomised controlled trial
Participants	53 formula milk-fed preterm 'small for gestational age' infants
Interventions	Postdischarge formula (energy content 74 kcal/100 mL, protein content 1.8 g/100 mL) (N = 24) vs standard term formula (Ross Similac With Fe) (N = 29) for 12 months post discharge
Outcomes	Growth parameters at 6, 9 and 12 months' corrected age
Notes	Published in abstract form only. Additional information and data courtesy of Dr Stephanie Atkinson

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was independently generated.
Allocation concealment (selection bias)	Low risk	Allocation was drawn from sequential sealed opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up growth parameter outcome assessments were completed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors were not aware of which formula milk infants received.

Carver 2001

Methods	Randomised controlled trial
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Carver 2001 (Continued)

Participants	125 preterm infants (birth weight < 1800 g or gestation < 37 weeks). Infants with severe bronchopulmonary dysplasia or cardiac, respiratory, gastrointestinal or other systemic diseases at time of discharge were not eligible to participate.
Interventions	Postdischarge formula (energy content 74 kcal/100 mL, protein content 1.9 g/100 mL, calcium and phosphorus content 78 mg/100 mL and 46 mg/100 mL, respectively) (N = 67) or standard term formula (energy content 68 kcal/100 mL, protein content 1.5 g/100 mL) (N = 56). The intention was for the allocated formula to be the main milk source from hospital discharge until 12 months' corrected age.
Outcomes	Growth parameters assessed at intervals until the end of the 12-month study period
Notes	Setting: multi-centre - 6 perinatal centres in North America

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method used to generate random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	No information on randomisation method was provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	31 of 67 in postdischarge formula group and 26 of 56 in standard term formula group left the study early (plus 2 other infants, who were randomised but did not take part in the study). Total loss of follow-up for growth parameters assessed at 12 months was 60% in the intervention group and 52% in the control group. Infants exited the study early (without growth parameters measured) for a variety of reasons, including study non-compliance (not defined or described), gastrointestinal upset and "illness unrelated to the study feedings" (not defined or described).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of which formula milk infants received.

Cooke 2001

Methods	Randomised controlled trial
Participants	103 preterm infants (birth weight < 1750 g or gestation < 35 weeks). Only infants who were 'growing normally' (rate of weight gain > 25 g/kg/d) at the time of discharge were eligible to participate.
Interventions	Preterm formula (energy content 80 kcal/100 mL, protein content 2.2 g/100 mL, calcium and phosphorus content 108 mg/100 mL and 54 mg/100 mL, respectively) (N = 49) or standard term formula (energy content 66 kcal/100 mL, protein content 1.4 g/100 mL) (N = 54) from hospital discharge until 6 months' corrected age

Cooke 2001 (Continued)

Outcomes	Anthropometric and developmental parameters (including Bayley Scales of Infant Development II), measures of bone mineralisation
Notes	Setting: Royal Victoria Hospital, Newcastle upon Tyne, UK Research supported by Nutricia (formula milk manufacturer) Article reported growth data for boys and girls separately. We combined data for inclusion in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was centrally generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was near complete (> 80%).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of which formula milk infants received.

De Curtis 2002

Methods	Randomised controlled trial
Participants	33 formula milk-fed preterm infants (birth weight < 1750 g or gestation < 35 weeks)
Interventions	Postdischarge formula (energy content 74 kcal/100 mL, protein content 1.8 g/100 mL, calcium and phosphorus content 80 mg/100 mL and 40 mg/100 mL, respectively) (N = 16) or standard term formula (energy content 66 kcal/100 mL, protein content 1.4 g/100 mL) (N = 17) from hospital discharge until 2 months' corrected age
Outcomes	Growth parameters and bone mineralisation measured by dual-energy X-ray absorptiometry at the end of the 2-month study period
Notes	Setting: Department of Pediatrics, University of Liege, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence was not described.

De Curtis 2002 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information on randomisation method was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was near complete (> 90%).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of which formula milk infants received.

Jeon 2011

Methods	Randomised controlled trial
Participants	59 preterm very low birth weight infants
Interventions	Preterm formula (energy content 80 kcal/100 mL, protein content 2.3 g/100 mL, calcium and phosphorus content 128 mg/100 mL and 64 mg/100 mL, respectively) (N = 34) or standard term formula (energy content 67 kcal/100 mL, protein content 1.6 g/100 mL) (N = 34) from hospital discharge until 3 months post term, then both groups continued with standard term formula until at least 6 months post term
Outcomes	Growth parameters at 3-monthly intervals until 18 months post term, Bayley Scales of Infant Development II at 18 months' corrected age
Notes	<p>Setting: multi-centre trial in 4 hospitals in South Korea</p> <p>Research supported by Maeli Dairy Industry Co. Ltd. (formula milk manufacturer)</p> <p>Initially, 3 groups were randomly allocated to receive (1) standard term formula, (2) preterm formula for 3 months or (3) preterm formula for 6 months. However, results showed substantial and significant between-group differences in baseline demographic characteristics, especially between group (3) and the other groups. Group (3) infants had statistically significantly lower birth weight and were more likely to be small for gestational age. We therefore chose to discard data from this arm and to restrict comparison of outcomes to group (1) vs group (3).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	No information on randomisation method was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Growth outcome data to 18 months were available for 30 (88%) intervention group and 29 (85%) control group infants.

Jeon 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Families and caregivers were likely to have been aware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors may have been aware of which formula milk infants received.

Koo 2006

Methods	Randomised controlled trial
Participants	89 preterm infants ready for hospital discharge (gestational age at birth < 35 weeks). Infants with major congenital malformation, previous gastrointestinal surgery or abnormal suck and swallow actions were not eligible to participate.
Interventions	Nutrient-enriched formula (energy content 74 kcal/100 mL, protein content 1.9 g/100 mL, calcium and phosphorus content 78 mg/100 mL and 46 mg/100 mL, respectively) (N = 44) or standard term formula (energy content 67 kcal/100 mL, protein content 1.5 g/100 mL) (N = 45). The intention was for the allocated formula to be fed ad libitum until 12 months after discharge.
Outcomes	Growth parameters and bone mineral content at intervals until the end of the 12-month study period
Notes	Setting: Department of Pediatrics, Wayne State University, and Hutzel Hospital, Detroit, Michigan, USA Research supported by Ross Products Division, Abbott Laboratories (formula milk manufacturer)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence was not described.
Allocation concealment (selection bias)	Low risk	Allocation was drawn from sequential sealed opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Growth outcome data to 12 months were available for 31 (70%) intervention group and 36 (80%) control group infants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of which formula milk infants received.

Litmanovitz 2004

Methods	Randomised controlled trial
Participants	20 healthy very low birth weight infants at hospital discharge
Interventions	Nutrient-enriched formula (energy content 74 kcal/100 mL, protein content 1.9 g/100 mL) (N = 10) or standard term formula (energy content 67 kcal/100 mL, protein content 1.5 g/100 mL) (N = 10) after hospital discharge. Formula was intended to provide sole milk intake up to 6 months' corrected age.
Outcomes	Weight, length, head circumference and measures of bone mineralisation at term and at 6 months' corrected age
Notes	Setting: Meir General Hospital, Kfar-saba, Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	No information on randomisation method was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was near complete (> 80%).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided on whether families and caregivers were aware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided on whether outcome assessors were aware of which formula milk infants received.

Lucas 1992

Methods	Randomised controlled trial
Participants	32 exclusively formula milk-fed preterm infants, birth weight < 1850 g, weight < 3000 g at hospital discharge
Interventions	Nutrient-enriched formula (energy content 72 kcal/100 mL, protein content 1.8 g/100 mL, calcium and phosphorus content 70 mg/100 mL and 35 mg/100 mL, respectively) (N = 16) or standard term formula (energy content 68 kcal/100 mL, protein content 1.4 g/100 mL) (N = 16) after hospital discharge. Formula was intended to provide sole milk intake up to 9 months' corrected age.
Outcomes	Measures of growth (weight, crown-heel length and head circumference), feed tolerance, bone mineralisation during trial period
Notes	Setting: Department of Paediatrics, Rosie Maternity Hospital, Cambridge Research supported by Farley Health Products (formula milk company) One infant who was randomised to the standard term formula group was transferred to another hospital before planned hospital discharge and could not be included in follow-up assessments.

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

Lucas 1992 (Continued)

Data were presented graphically. We extracted numerical data (mean and SD) from the graphs to calculate mean differences.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	No information on randomisation method was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was near complete (1 infant from the standard term formula group was withdrawn).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It is likely that families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It is likely that outcome assessors were unaware of which formula milk infants received.

Lucas 2001

Methods	Randomised controlled trial
Participants	229 formula milk-fed preterm infants, birth weight < 1750 g, weight < 3000 g at hospital discharge
Interventions	Nutrient-enriched formula (energy content 72 kcal/100 mL, protein content 1.85 g/100 mL, calcium and phosphorus content 70 mg/100 mL and 35 mg/100 mL, respectively) (N = 113) or standard term formula (energy content 68 kcal/100 mL, protein content 1.5 g/100 mL) (N = 116) from hospital discharge until 9 months post term
Outcomes	Growth parameters up to 18 months post term, neurodevelopment (Bayley Scales) at 18 months' corrected age
Notes	Setting: 5 neonatal centres in the UK (1993-1995) Research supported by Farley Health Products (formula milk company)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A member of the clinical team not involved in the trial prepared randomisation assignments.
Allocation concealment (selection bias)	Low risk	Allocation was drawn from sequential sealed opaque envelopes.
Incomplete outcome data (attrition bias)	Low risk	Growth and developmental outcomes were assessed in > 80% of participating infants.

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

Lucas 2001 (Continued)

All outcomes

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were unaware of which formula milk infants received.

Peng 2004

Methods	Randomised controlled trial
Participants	34 preterm infants with gestational age of ≤ 35 weeks and birth weight ≤ 1850 g
Interventions	Nutrient-enriched formula (energy content 81 kcal/100 mL, protein content 2.40 g/100 mL, calcium and phosphorus content 95 mg/100 mL and 53 mg/100 mL, respectively) (N = 19) or standard term formula (energy content 67.6 kcal/100 mL, protein content 1.4 g/100 mL) (N = 15) from hospital-discharge until 6 months' corrected age
Outcomes	Measures of growth (weight, crown-heel length and head circumference), feed tolerance, bone mineralisation during trial period
Notes	Setting: Mackay Memorial Hospital, Taipei, Taiwan Research supported by Mead Johnson (formula milk company) No differences were found between the 2 groups in weight, length or head circumference at baseline or on follow-up. Infants fed premature formula had higher blood urea nitrogen and phosphorus at 3 months' corrected age. Those on the premature formula also had higher energy intake at 1 month corrected age.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	No information on randomisation method was provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Growth outcome data to 6 months were available for 29 of the 40 infants initially enrolled (73%).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Families and caregivers were likely to have been aware of which formula milk infants received, as parents were not blinded to infant assignment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors may have been aware of which formula milk infants received, as physicians were not blinded to infant assignment.

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

Picaud 2005

Methods	Randomised controlled trial
Participants	49 formula milk-fed preterm infants, birth weight < 1750 g or gestation at birth < 33 weeks
Interventions	Preterm formula (energy content 81 kcal/100 mL, protein content 2.3 g/100 mL, calcium and phosphorus content 100 mg/100 mL and 53 mg/100 mL, respectively) (N = 23) or standard term formula (energy content 67 kcal/100 mL, protein content 1.7 g/100 mL) (N = 26) from hospital discharge until 2 months post term
Outcomes	Growth parameters and measures of bone mineralisation up to 4 months' corrected age
Notes	Setting: 2 tertiary care neonatal units in France (2001-2004) Research supported by Nestlé France (formula milk manufacturer) From 2 months post discharge, both groups received standard term formula milk.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Clinical trials unit was generated.
Allocation concealment (selection bias)	Low risk	Pharmacy was coded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up by 12 months in the control group was substantial (35%) and was greater than in the intervention group (9%).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and caregivers were unaware of which formula milk infants received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were unaware of which formula milk infants received.

Roggero 2011

Methods	Randomised controlled trial
Participants	123 formula fed preterm infants who were 'appropriate (birth weight) for gestational age'
Interventions	Postdischarge formula (energy content 75 kcal/100 mL, protein content 2.0 g/100 mL, calcium and phosphorus content 100 mg/100 mL and 56 mg/100 mL, respectively) (N = 59) or standard term formula (energy content 67 kcal/100 mL, protein content 1.4 g/100 mL) (N = 64) from hospital discharge until 6 months' corrected age
Outcomes	Growth parameters and fat mass up to (at least) 12 months' corrected age

Roggero 2011 (Continued)

Notes Trial was registered with Current Controlled Trials (<http://www.controlledtrials.com/ISRCTN30189842>).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by an independent investigator using computer-generated randomisation lists.
Allocation concealment (selection bias)	Low risk	Randomisation was performed by an independent investigator using computer-generated randomisation lists.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up until 12 months post term was complete.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided.

Roggero 2012

Methods	Randomised controlled trial
Participants	84 formula milk-fed preterm infants born 'small for gestational age' (< 10th percentile)
Interventions	Postdischarge formula (energy content 75 kcal/100 mL, protein content 2.0 g/100 mL, calcium and phosphorus content 100 mg/100 mL and 56 mg/100 mL, respectively) (N = 40) or standard term formula (energy content 67 kcal/100 mL, protein content 1.4 g/100 mL) (N = 44) from hospital discharge until 6 months' corrected age
Outcomes	Growth parameters and fat mass up to 6 months' corrected age
Notes	Setting: Neonatal Intensive Care Unit, Department of Maternal and Paediatric Sciences, Milan, Italy (2008-2010) These trialists also conducted an RCT of nutrient-enriched vs standard formula in appropriate for gestational age infants (N = 123). These data are not yet published or available from study authors (referred to in conference abstract: Roggero 2011c).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was provided.
Allocation concealment (selection bias)	Unclear risk	No information was provided.
Incomplete outcome data (attrition bias)	Low risk	Follow-up until 6 months post term was complete.

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

Roggero 2012 (Continued)

All outcomes

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided.

Taroni 2009

Methods	Randomised controlled trial
Participants	27 formula milk-fed preterm infants, birth weight < 1500 g or gestation at birth < 33 weeks, 'small for gestational age' (< 10th percentile)
Interventions	Postdischarge formula (energy content 75 kcal/100 mL, protein content 2.0 g/100 mL, calcium and phosphorus content 100 mg/100 mL and 56 mg/100 mL, respectively) (N = 14) or standard term formula (energy content 67 kcal/100 mL, protein content 1.4 g/100 mL) (N = 13) from hospital discharge until 1 month corrected age
Outcomes	Growth parameters and fat mass up to 1 month corrected age
Notes	Setting: 4 Italian neonatal units (2008-2009)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was pre-prepared.
Allocation concealment (selection bias)	Unclear risk	No information was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up until 1 month post term was complete.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided.

PMA: postmenstrual age.

RCT: randomised controlled trial.

VLBW: very low birth weight.

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

Study	Reason for exclusion
Amesz 2010	The protein content of both formula milks was ≤ 1.7 g/100 mL.
Bernbaum 1989	The energy content of both formula milks was < 70 kcal/100 mL.
Bhatia 1991	The protein content of both formula milks was ≤ 1.7 g/100 mL.
Brunton 1998	Both formula milks were calorie-enriched (90 kcal/100 mL).
Chan 1994	The energy content of both formula milks was < 70 kcal/100 mL.
Cooper 1985	The energy content of both formula milks was < 70 kcal/100 mL.
Friel 1993	The energy content of both formula milks was < 70 kcal/100 mL.
Lapillonne 2004	Both formula milks were calorie-enriched (81 kcal/100 mL) and protein-enriched (> 2.0 g/100 mL).
Wheeler 1996	The energy content of both formula milks was < 70 kcal/100 mL.

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

[Ekcharoen 2015](#)

Methods	Randomised controlled trial
Participants	Preterm infants who had postconceptional age 35 to 36 weeks and weight 1.8 to 3 kg at hospital discharge
Interventions	Postdischarge formula vs high-energy, high-protein, medium-chain triglyceride-containing formula
Outcomes	Growth rate at days 28, 56 and 84 after hospital discharge
Notes	Abstract only; full-text article not available (study authors contacted September 2016)

DATA AND ANALYSES

Comparison 1. Postdischarge formula versus standard term formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth rates during trial period	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Weight gain (g/kg/d)	1	33	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.37, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Linear growth (mm/wk)	1	33	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.07, 1.07]
1.3 Head circumference (mm/wk)	1	33	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.68, 0.68]
2 Weight (grams)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 3-4 months post term	6	523	Mean Difference (IV, Fixed, 95% CI)	-7.45 [-141.84, 126.93]
2.2 6 months post term	7	576	Mean Difference (IV, Fixed, 95% CI)	35.54 [-113.71, 184.78]
2.3 9 months post term	4	347	Mean Difference (IV, Fixed, 95% CI)	244.09 [16.95, 471.23]
2.4 12 months post term	4	314	Mean Difference (IV, Fixed, 95% CI)	-14.87 [-243.18, 213.43]
2.5 18-24 months post term	1	192	Mean Difference (IV, Fixed, 95% CI)	100.0 [-246.90, 446.90]
3 Crown-heel length (mm)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 3-4 months post term	6	523	Mean Difference (IV, Fixed, 95% CI)	2.45 [-2.01, 6.90]
3.2 6 months post term	7	576	Mean Difference (IV, Fixed, 95% CI)	2.12 [-2.16, 6.41]
3.3 9 months post term	4	347	Mean Difference (IV, Fixed, 95% CI)	7.33 [1.80, 12.87]
3.4 12 months post term	4	314	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-6.43, 5.10]
3.5 18-24 months post term	1	192	Mean Difference (IV, Fixed, 95% CI)	9.0 [0.32, 17.68]
4 Head circumference (mm)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 3-4 months post term	6	523	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.86, 2.26]
4.2 6 months post term	7	576	Mean Difference (IV, Fixed, 95% CI)	2.28 [-0.28, 4.83]
4.3 9 months post term	4	347	Mean Difference (IV, Fixed, 95% CI)	0.16 [-3.21, 3.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 12 months post term	4	314	Mean Difference (IV, Fixed, 95% CI)	2.11 [-1.52, 5.75]
4.5 18-24 months post term	1	192	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-8.24, 2.24]
5 Development	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Bayley Scales of Infant Development II: Mental Development Index	1	184	Mean Difference (IV, Fixed, 95% CI)	0.90 [-3.24, 5.04]
5.2 Bayley Scales of Infant Development II: Psychomotor Development Index	1	184	Mean Difference (IV, Fixed, 95% CI)	2.70 [-1.28, 6.68]
6 Bone mineralisation	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Bone area at 2 months post term (cm ²)	1	33	Mean Difference (IV, Fixed, 95% CI)	7.0 [-15.46, 29.46]
6.2 Bone mineral content at 2 months post term (grams)	1	33	Mean Difference (IV, Fixed, 95% CI)	3.20 [-4.73, 11.13]
6.3 Bone 'speed of sound' as assessed on ultrasonography at 6 months post term (mm/s)	1	20	Mean Difference (IV, Fixed, 95% CI)	45.0 [-18.48, 108.48]
6.4 Bone specific serum alkaline phosphatase at 6 months post term (units/L)	1	20	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-42.01, 24.01]
6.5 Bone width at 9 months post term (cm)	1	31	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.11]
6.6 Bone mineral content at 9 months post term (mg/cm)	1	31	Mean Difference (IV, Fixed, 95% CI)	20.60 [7.78, 33.42]

Analysis 1.1. Comparison 1 Postdischarge formula versus standard term formula, Outcome 1 Growth rates during trial period.

Analysis 1.2. Comparison 1 Postdischarge formula versus standard term formula, Outcome 2 Weight (grams).

Analysis 1.3. Comparison 1 Postdischarge formula versus standard term formula, Outcome 3 Crown-heel length (mm).

Analysis 1.4. Comparison 1 Postdischarge formula versus standard term formula, Outcome 4 Head circumference (mm).

Analysis 1.5. Comparison 1 Postdischarge formula versus standard term formula, Outcome 5 Development.

Study or subgroup	Post-dis-charge formula		Term formula		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Test for subgroup differences: $\chi^2=0.38$, $df=1$ ($P=0.54$), $I^2=0\%$							

Favours term formula

-5 -2.5 0 2.5 5

Favours postdischarge for

Analysis 1.6. Comparison 1 Postdischarge formula versus standard term formula, Outcome 6 Bone mineralisation.

Study or subgroup	Post-dis-charge formula		Term formula		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.6.1 Bone area at 2 months post term (cm²)							
De Curtis 2002	16	351 (21)	17	344 (42)		100%	7[-15.46,29.46]
Subtotal ***	16		17			100%	7[-15.46,29.46]
Heterogeneity: Not applicable Test for overall effect: $Z=0.61$ ($P=0.54$)							
1.6.2 Bone mineral content at 2 months post term (grams)							
De Curtis 2002	16	68.2 (10.6)	17	65 (12.6)		100%	3.2[-4.73,11.13]
Subtotal ***	16		17			100%	3.2[-4.73,11.13]
Heterogeneity: Not applicable Test for overall effect: $Z=0.79$ ($P=0.43$)							
1.6.3 Bone 'speed of sound' assessed on ultrasonography at 6 months post term (mm/s)							
Litmanovitz 2004	10	3032 (60)	10	2987 (83)		100%	45[-18.48,108.48]
Subtotal ***	10		10			100%	45[-18.48,108.48]
Heterogeneity: Not applicable Test for overall effect: $Z=1.39$ ($P=0.16$)							
1.6.4 Bone specific serum alkaline phosphatase at 6 months post term (units/L)							
Litmanovitz 2004	10	125 (41)	10	134 (34)		100%	-9[-42.01,24.01]
Subtotal ***	10		10			100%	-9[-42.01,24.01]
Heterogeneity: Not applicable Test for overall effect: $Z=0.53$ ($P=0.59$)							
1.6.5 Bone width at 9 months post term (cm)							
Lucas 1992	16	0.7 (0.1)	15	0.6 (0.1)		100%	0.05[-0.01,0.11]
Subtotal ***	16		15			100%	0.05[-0.01,0.11]
Heterogeneity: Not applicable Test for overall effect: $Z=1.55$ ($P=0.12$)							
1.6.6 Bone mineral content at 9 months post term (mg/cm)							
Lucas 1992	16	115.3 (21.6)	15	94.7 (14.3)		100%	20.6[7.78,33.42]
Subtotal ***	16		15			100%	20.6[7.78,33.42]
Heterogeneity: Not applicable Test for overall effect: $Z=3.15$ ($P=0$) Test for subgroup differences: $\chi^2=13.06$, $df=1$ ($P=0.02$), $I^2=61.71\%$							

Favours term formula

-100 -50 0 50 100

Favours postdischarge for

Comparison 2. Preterm formula versus standard term formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth rates during trial period	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Weight gain (g/d)	1	42	Mean Difference (IV, Fixed, 95% CI)	3.70 [-0.16, 7.56]
1.2 Linear growth (mm/wk)	1	42	Mean Difference (IV, Fixed, 95% CI)	1.0 [0.09, 1.91]
1.3 Head circumference (mm/wk)	1	42	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.04, 1.04]
2 Weight (grams)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 3-4 months post term	3	130	Mean Difference (IV, Fixed, 95% CI)	74.41 [-267.10, 415.93]
2.2 6 months post term	4	273	Mean Difference (IV, Fixed, 95% CI)	74.60 [-164.73, 313.92]
2.3 9 months post term	1	59	Mean Difference (IV, Fixed, 95% CI)	112.0 [-482.69, 706.69]
2.4 12 months post term	4	265	Mean Difference (IV, Fixed, 95% CI)	539.48 [255.03, 823.92]
2.5 18 months post term	2	162	Mean Difference (IV, Fixed, 95% CI)	490.81 [142.19, 839.44]
3 Crown-heel length (mm)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 3-4 months post term	3	130	Mean Difference (IV, Fixed, 95% CI)	-2.27 [-13.09, 8.56]
3.2 6 months post term	3	160	Mean Difference (IV, Fixed, 95% CI)	1.83 [-6.25, 9.92]
3.3 9 months post term	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-17.03, 11.03]
3.4 12 months post term	3	152	Mean Difference (IV, Fixed, 95% CI)	5.13 [-4.23, 14.49]
3.5 18 months post term	2	162	Mean Difference (IV, Fixed, 95% CI)	11.00 [1.89, 20.11]
4 Head circumference (mm)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 3-4 months post term	3	130	Mean Difference (IV, Fixed, 95% CI)	3.61 [-2.09, 9.31]
4.2 6 months post term	3	160	Mean Difference (IV, Fixed, 95% CI)	5.82 [1.32, 10.32]
4.3 9 months post term	1	59	Mean Difference (IV, Fixed, 95% CI)	8.0 [0.85, 15.15]
4.4 12 months post term	3	152	Mean Difference (IV, Fixed, 95% CI)	6.07 [1.07, 11.06]
4.5 18 months post term	2	162	Mean Difference (IV, Fixed, 95% CI)	5.42 [0.69, 10.14]
5 Development	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Bayley Scales of Infant Development II: Mental Development Index	2	143	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-6.22, 3.35]
5.2 Bayley Scales of Infant Development II: Psychomotor Development Index	2	143	Mean Difference (IV, Fixed, 95% CI)	-1.13 [-4.19, 1.93]

Analysis 2.1. Comparison 2 Preterm formula versus standard term formula, Outcome 1 Growth rates during trial period.

Analysis 2.2. Comparison 2 Preterm formula versus standard term formula, Outcome 2 Weight (grams).

Analysis 2.3. Comparison 2 Preterm formula versus standard term formula, Outcome 3 Crown-heel length (mm).

Analysis 2.4. Comparison 2 Preterm formula versus standard term formula, Outcome 4 Head circumference (mm).

Analysis 2.5. Comparison 2 Preterm formula versus standard term formula, Outcome 5 Development.

WHAT'S NEW

Date	Event	Description
8 September 2016	New citation required but conclusions have not changed	Search updated; 1 new trial added; conclusion unchanged

Date	Event	Description
8 September 2016	New search has been performed	One new trial added (Roggero 2011)

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 2, 2005

Date	Event	Description
28 October 2011	New citation required and conclusions have changed	Updated search; included 8 new trials as reported by trial authors Revised review structure; specified separate comparisons of preterm formula and postdischarge formula vs standard term formula Modified conclusions Added new review authors
28 October 2011	New search has been performed	This updates the review, "Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge" (McGuire 2007).
28 April 2008	Amended	Converted to new review format
25 June 2007	New citation required but conclusions have not changed	Made substantive amendments

CONTRIBUTIONS OF AUTHORS

William McGuire and Lauren Young undertook the electronic search and identified citations for possible inclusion. Lauren Young, William McGuire and Nick Embleton reviewed the citation list (title and abstract) for inclusion and undertook methodological appraisal and data extraction, entry and analysis. William McGuire acted as an arbiter for disagreements, reviewed data entered and analysed and completed the review.

DECLARATIONS OF INTEREST

Nick Embleton has conducted research with support from manufacturers of infant formula including Nestec SA (Switzerland), Wyeth UK and Nutricia UK, but did not receive payment, support nor benefit in kind for contributions to this review.

SOURCES OF SUPPORT

Internal sources

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

External sources

- NIHR, UK.

This report is independent research funded by a UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the review authors and are not necessarily those of the NHS, the NIHR or the UK Department of Health.

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been provided by Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the methods and plan for Summary of findings tables and GRADE recommendations, which were not included in the original protocol nor in the previously published review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula [standards]; Child Development [*physiology]; Dietary Proteins [administration & dosage]; Energy Intake [*physiology]; Infant Nutritional Physiological Phenomena; Infant, Low Birth Weight [growth & development]; Infant, Premature [*growth & development]; Patient Discharge; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant; Infant, Newborn