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[Intervention Review]

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

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ABSTRACT

Background

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

Objectives

To determine the effect of feeding nutrient-enriched formula compared with standard term formula on growth and development for preterm infants following hospital discharge.

Search strategy

The standard search strategy of the Cochrane Neonatal Review Group were used. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE (1966 - May 2007), EMBASE (1980 - May 2007), CINAHL (1982 - May 2007), conference proceedings, and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials that compared the effect of feeding preterm infants following hospital discharge with nutrient-enriched formula compared with standard term formula.

Data collection and analysis

Data was extracted using the standard methods of the Cochrane Neonatal Review Group, with separate evaluation of trial quality and data extraction by two authors, and synthesis of data using weighted mean difference and a fixed effects model for meta-analysis.

Main results

Seven trials were found that were eligible for inclusion. These recruited a total of 631 infants and were generally of good methodological quality. The trials found little evidence that feeding with nutrient-enriched formula milk affected growth and development. Because of differences in the way individual trials measured and presented outcomes, data synthesis was limited. Growth data from two trials found that, at six months post-term, infants fed with nutrient-enriched formula had statistically significantly lower weights [weighted mean difference: -601 (95% confidence interval -1028, -174) grams], lengths [-18.8 (-30.0, -7.6) millimetres], and head circumferences [-10.2 (-18.0, -2.4) millimetres], than infants fed standard term formula. At 12 to 18 months post-term, meta-analyses of data from three trials did not find any statistically significant differences in growth parameters. However, examination of these meta-analyses demonstrated statistical heterogeneity. Meta-analyses of data from two trials did not reveal a statistically significant difference in Bayley Mental Development or Psychomotor Development Indices. There are not yet any data on growth or development through later childhood.

Authors' conclusions

The available data do not provide strong evidence that feeding preterm infants following hospital discharge with nutrient-enriched formula compared with standard term formula affects growth rates or development up to 18 months post-term.

PLAIN LANGUAGE SUMMARY

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

Preterm infants are often much smaller than term infants by the time that they are discharged home from hospital. This review attempted to identify evidence that feeding these infants with formula milk enriched with nutrients rather than ordinary formula designed for term infants, would increase growth rates and benefit development. Seven good quality trials were identified. These trials provided little evidence that unrestricted feeding with nutrient-enriched formula milk affects growth and development up to about 18 months of age. Long-term growth and development has not yet been assessed. Further randomised controlled trials are needed to address this question.

BACKGROUND

Compared with term infants, preterm infants have very limited nutrient reserves at birth. Preterm infants are additionally subject to a variety of physiological and metabolic stresses, such as infection or respiratory distress, that increase their nutritional needs. An international consensus group has recommended nutritional requirements for preterm infants based on data from intrauterine growth and nutrient balance studies (Tsang 1993). These recommendations assume that the optimal rate of postnatal growth for preterm infants should be about the same as that of normal fetuses of an equivalent post-conceptional age. However, evidence exists that in practice these target levels of nutrient input are rarely achieved. Most preterm infants accumulate significant energy, protein, mineral, and other nutrient deficits by the time of discharge from hospital (Embleton 2001).

Preterm infants are typically discharged from hospital when they weigh between about 1.8 and 2.2 kilograms. At this stage, many preterm infants are significantly growth restricted (Lucas 1984). In a multicentre study of more than 24000 preterm infants cared for in 124 neonatal intensive care units in North America between 1997 and 2000, the prevalence of extrauterine growth restriction at hospital discharge, defined as lying below the tenth percentile of the predicted value based on intrauterine growth expectation, was 28% for weight, 34% for length, and 16% for head circumference. For each parameter, the risk of growth restriction increased with decreasing gestational age and birth weight (Clark 2003).

Following hospital discharge, demand fed preterm infants consume greater volumes of milk than term infants in order to attain some "catch up" growth (Lucas 1992a). However, nutritional and growth deficits persist throughout childhood (Morley 2000; Ford 2000). Poor postnatal growth in preterm infants, especially of the head, is associated with an increased risk of neurodevelopmental impairment in later childhood, as well as with poorer cognitive and educational outcomes (Hack 1991; Cooke 2003). Preterm infants who have accumulated deficits in calcium and phosphate by the time of hospital discharge are at increased risk of poor bone mineralisation, metabolic bone disease, and a reduced rate of skeletal growth compared to infants born at term (Rigo 2000). There has also been concern that nutritional deficiency and growth restriction both in utero and in the early neonatal period may have consequences for cardiovascular disease risk factors such as blood pressure, insulin resistance, and obesity, and for long term cardiovascular health (Barker 2002). However, whether a real causal association exists remains unclear at present (Huxley 2002).

A variety of strategies are available for improving nutrient input in preterm infants prior to hospital discharge. Several interventions including fortification of human breast milk and the use of nutrient-enriched formula milk have been assessed in other Cochrane reviews (Bell 2003; Kuschel 2003; McGuire 2003a; McGuire 2003b). There is also an increasing awareness that there is an opportunity for continued nutritional intervention during the post-hospital discharge period of early infancy (Cooke 2000; Griffin 2002). Nutritional supplementation during this period may be of particular importance for infants with ongoing additional metabolic requirements, for example due to chronic lung disease. It is important to determine whether nutritional supplementation following hospital discharge can improve important outcomes for preterm infants.

Although human breast milk is the recommended source of nutrition for young infants (54th WHA), many preterm infants, and particularly very preterm infants, receive formula milk as a major source of nutrition in the first few months following hospital discharge. A variety of formula feeds, mainly modified cow's milk, are available (Fewtrell 1999). These vary with regard to calorie, protein and mineral content and can be categorised broadly as:

1. Standard term formula; designed for term infants, based on the composition of mature breast milk. The typical energy content is 68 kcal/100 ml. The concentration of protein, approximately 1.4 to 1.5 grams/100 ml, and calcium and phosphate are not sufficient to provide the recommended nutrient needs for stable and growing preterm infants (Tsang 1993).

2. Preterm formula; energy-enriched (approximately 80 kcal/100 ml), protein-enriched (approximately 2.0 to 2.4 grams/100 ml), and variably enriched with minerals, vitamins, and trace elements to support intra-uterine nutrient accretion rates. These milks are often used for nutrition of preterm infants prior to hospital discharge.

3. Post-discharge formula; specifically designed for preterm infants post-discharge from hospital. These are less nutrient dense compared with preterm formulae, but are energy (about 72 to 74 kcal/100 ml), protein (about 1.8 grams/ 100 ml) -enriched, and variably enriched with minerals, vitamins, and trace elements compared to standard term formula milk.

The purpose of this review is to determine whether feeding preterm or low birth weight infants after hospital discharge with a nutrient-enriched formula milk versus a standard term formula improves growth and development. Whether feeding with nutrient-enriched formula milk is associated with any adverse effects is also examined. For example, feeding nutrient dense formula may reduce gastric motility and emptying (Hancock 1984; Siegel 1984). Nutrient-enriched formula milk may therefore be more poorly tolerated, so reducing nutrient delivery, and potentially removing any benefits for growth and development.

OBJECTIVES

To determine the effect of feeding preterm infants following hospital discharge with nutrient-enriched formula milk compared with standard term formula milk affects growth and development

In separate comparisons, nutrient-enriched formula milk versus standard term formula milk in babies fed formula milk exclusively, in human breast milk-fed babies fed formula as supplement, and in babies where the nutrient-enriched formula is used either as sole diet or as a supplement to breast milk were compared.

The following sub-group analyses were pre-specified:

1. Infants of very low birth weight (less than 1.5 kilograms) or who are very preterm at birth (less than 32 weeks).

2. Infants who remain small for gestational age (less than 10 th percentile for weight) at hospital discharge.

3. Infants with chronic lung disease requiring home supplemental oxygen therapy.

4. Comparisons of "preterm" formula (energy content between greater than 75 kcal/100 ml and protein content at least 2.0 grams/100 ml) versus standard term formula.

5. Comparisons of "post-discharge" formula (energy content between 72 and 75 kcal/100 ml and protein content at least 1.6 grams/100 ml, but less than 2.0 grams/100 ml) versus standard term formula.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random patient allocation. Studies published as abstracts were only eligible for inclusion if assessment of study quality was possible (either directly or after contact with the investigators) and if other criteria for inclusion were fulfilled.

Types of participants

Preterm infants (less than 37 weeks' gestation) at least partially formula milk-fed, following discharge from hospital. The intervention may have commenced up to one week prior to planned discharge from hospital. Trials that randomly assigned infants to calorie and protein-enriched formula milk versus standard term formula milk more than one week prior to hospital discharge (and then continued the intervention after hospital discharge) were not to be included in this review. These trials may be eligible for inclusion in the Cochrane review of preterm formula milk versus standard term formula milk for feeding preterm or low birth weight infants prior to hospital discharge (Bell 2003).

Types of interventions

Feeding with nutrient enriched formula milk (at least 72 kcal/100 ml, and at least 1.6 grams protein /100 ml) versus standard term formula milk (energy content less than 72 kcal/100 ml, and protein content less than 1.6 grams/100 ml). Nutrient-enriched formula milk may additionally be enriched with minerals, vitamins and trace elements. The formula milks may be fed either as sole diet or as a supplement to human milk. Infants in the trial groups should have received similar care other than the type of formula milk. For example, there should not have been any differences between groups in the prescription of target levels of volume of intake, or advice or support for demand feeding.

Types of outcome measures

Primary:
1. Growth:
(i) Rates of weight gain (grams per day, or grams per kilogram per day), linear growth (millimetres per week), head growth (millimetres per week), or skinfold thickness growth (millimetres per week) during the trial period.
(ii) Long-term growth- weight, height, or head circumference (and/or proportion of infants who remain below the tenth percentile for the index population's distribution) assessed at intervals from six months of age (corrected for preterm birth), to 18 months, and beyond.
2. Development:
(i) Neurodevelopmental outcomes at greater than, or equal to, 12 months of age (corrected for preterm birth) measured using validated assessment tools such as Bayley Scales of Infant Development
(ii) Severe neurodevelopmental disability defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment.
(iii) Cognitive and educational outcomes at aged more than five years old: Intelligence quotient and/or indices of educational achievement measured using a validated assessment tool (including school examination results).

Secondary:
3. Measures of bone mineralisation such as serum alkaline phosphatase level, or bone mineral content assessed by dual energy x ray absorptiometry, at the end of the trial period.
4. Feed intolerance such as vomiting or diarrhoea that necessitates ceasing the study formula milk.
5. Clinical or radiological evidence of rickets on long term follow up.
6. Blood pressure and body mass index on long term follow up.

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. This consisted of searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE (1966 - May 2007), and EMBASE (1980 - May 2007), and CINAHL (1982 - May 2007). The electronic search used the following text words and MeSH terms: [Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR infan* OR neonat*] AND "Infant-Nutrition"/ all subheadings OR Infant Formula OR milk OR formula]. The search outputs were limited with the relevant search filters for clinical trials. No language restriction was applied. References in previous reviews and studies were examined. Abstracts presented at the Society for Pediatric Research, European Society for Pediatric Research, the North American Society of Pediatric Gastroenterology and Nutrition, and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition between 1990 and 2006/7 were searched. Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria. The UK National Research Register (http://www.nrr.nhs.uk), and Current Controlled Trials (http://www.controlled-trials.com) websites were searched for completed or ongoing trials.

Data collection and analysis

1. William McGuire (WM) and Ginny Henderson (GH) screened the title and abstract of all studies identified by the above search strategy and obtained the full articles for all potentially relevant trials. WM and GH re-assessed independently the full text of these reports using an eligibility form based on the pre-specified inclusion criteria. Those studies that did not meet all of the inclusion criteria were excluded. Any disagreements were resolved by discussion until consensus was achieved.
2. WM and GH used the criteria and standard methods of the Cochrane Neonatal Review Group to assess independently the methodological quality of the included trials in terms of allocation concealment, blinding of parents or caregivers and assessors to intervention, and completeness of assessment in all randomised individuals. Where necessary, additional information was requested from trial authors to clarify methodology and results.
3. WM and GH used a data collection form to aid extraction of relevant information and data from each included study. Each reviewer extracted the data separately, compared data, and resolved differences by discussion until consensus was achieved. If data from the trial reports were insufficient, the authors were contacted for further information.
4. Outcomes for continuous data are presented using the weighted mean difference with 95% confidence interval. No categorical data are presented.
5. The treatment effects of individual trials and heterogeneity between trial results were examined by inspecting the forest plots and quantifying the impact of heterogeneity in any meta-analysis us-

ing a measure of the degree of inconsistency in the studies' results (I^2 statistic). If statistical heterogeneity was detected, the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) were explored using post hoc sub group analyses. A fixed effects model was used for meta-analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Seven trials were identified that fulfilled the eligibility criteria (Carver 2001; Cooke 2001; De Curtis 2002; Koo 2006; Litmanovitz 2004; Lucas 1992; Lucas 2001). These trials are described in the table, Characteristics of Included Studies. Six studies were excluded (Agosti 2003; Bhatia 1991; Brunton 1998; Chan 1994; Cooper 1985; Wheeler 1996). The reasons for exclusion are listed in the table, Characteristics of Excluded Studies. Three further reports of potentially eligible trials were identified (Atkinson 1999; Atkinson 2004; Picaud 2005). These have only been reported in abstract form. Further clarification of a number of issues is needed to determine if these may be included in an update of this review.

All of the included studies were undertaken since the late 1980s by investigators attached to perinatal centres in Europe, Israel, or North America. 631infants in total participated in the trials. Participating infants were of birth weight less than 1500 grams in one study (Litmanovitz 2004), 1750 grams in three studies (Cooke 2001; De Curtis 2002; Lucas 2001), 1800 grams in one study (Carver 2001), and 1850 grams in one study (Lucas 1992). In six trials (Carver 2001; De Curtis 2002; Koo 2006; Litmanovitz 2004; Lucas 1992; Lucas 2001), the energy content of the nutrient-enriched formula milks ranged from 72 to 74 kcal/100ml and the protein content from 1.8 to 1.9 grams/100ml ("post-discharge formula"). In the other trial (Cooke 2001), the intervention milk contained 80 kcal/100ml and 2.2 grams of protein per 100ml ("preterm formula"). The standard term formula in all of the trials contained 66 to 68 kcal/100ml and 1.4 to 1.5 grams of protein per 100ml. All of the participating infants were exclusively formula-fed ad libitum. These feeds were intended to be the principal source of milk for two months post-term (De Curtis 2002), six months post-term (Cooke 2001; Litmanovitz 2004), up to nine months post-term (Lucas 1992; Lucas 2001), or up to 12 months post-term (Carver 2001; Koo 2006).

The main outcomes assessed were growth parameters (weight, length, and occipito-frontal head circumference), feed tolerance, and measures of bone mineralisation. Two trials assessed neurodevelopmental outcomes beyond infancy using Bayley Scales of Infant Development II (Cooke 2001; Lucas 2001).

Risk of bias in included studies

In general, the methodological quality of the included studies was good, although only one trial report explicitly explained the method of randomisation (Lucas 2001). In the other trials, it is not clear whether allocation concealment was adequate. One trial was reported in abstract form only (Litmanovitz 2004). All of the trials blinded investigators and caregivers to the type of milk that the infant received. Five of the trials achieved complete or near-complete follow-up (Cooke 2001; De Curtis 2002; Koo 2006; Litmanovitz 2004; Lucas 1992; Lucas 2001). There was substantial loss to follow-up in one trial (Carver 2001).

Effects of interventions

NUTRIENT-ENRICHED FORMULA VS. STANDARD TERM FORMULA

PRIMARY OUTCOMES:

Growth (Outcomes 01.01- 01.04)

Carver 2001 reported higher rates of growth during the trial period in nutrient-enriched formula milk group. There was substantial loss to follow-up during the trial. The published report does not state how many infants were assessed at the various time points. The data could not be used to calculate mean differences. Cooke 2001 did not find a statistically significant difference in rate of weight gain during the trial period. These data were presented in graphs only and were not able to be extracted to allow calculation of the mean difference. At 18 months post-term, the nutrient-enriched formula group was statistically significantly heavier than the control group [mean difference: 500 (95% confidence interval 25, 974) grams], but there were not any statistically significant differences in length or head circumference. De Curtis 2002 did not find any statistically significant differences in the rate of gain of weight, length, or head circumference during the two months trial period. Koo 2006 reported that the mean weight, head circumference, and length was lower in the nutrient-enriched formula group at six, nine, and twelve months after hospital discharge. Lucas 1992 reported statistically significantly higher rates of weight gain and linear growth in infants who received nutrient-enriched formula milk during the nine months trial period. There was no statistically significant difference in the rate of head growth. These data were presented graphically. Relevant data could not be extracted in order to calculate mean differences. Lucas 2001 reported that at completion of the intervention period (nine months post-term), weight and length were statistically significantly greater in infants who received nutrient-enriched formula milk but that there was not a statistically significant difference in head circumference. At 18 months, there were not any statistically significant differences in weight or head circumference. The group of infants who received nutrient-enriched formula milk remained statistically significantly longer on average than the control group [mean difference 9.0 (95% confidence interval 0.3 to 17.7) millimetres]. Litmanovitz 2004 did not find any statistically significant difference in the weight, length, or head circumference at six months post-term.

Meta-analyses of growth data from two trials (Koo 2006; Litmanovitz 2004) found that, at six months post-term, infants fed with nutrient-enriched formula had statistically significantly lower weights [weighted mean difference: -601 (95% confidence interval -1028, -174) grams], lengths [weighted mean difference: -18.8 (95% confidence interval -30.0, -7.6) millimetres], and head circumferences [weighted mean difference: -10.2 (95% confidence interval -18.0, -2.4) millimetres], than infants fed standard term formula. At nine months post-term, meta-analyses of data from two trials (Koo 2006; Lucas 2001) did not find any statistically significant differences in growth parameters. At 12 - 18 months post-term, meta-analyses of data from three trials (Cooke 2001; Koo 2006; Lucas 2001) did not find any statistically significant differences in growth parameters. However, these meta-analyses demonstrated statistical heterogeneity.

Subgroup analyses of only the two trials that used "post-discharge" formula milk (Koo 2006; Lucas 2001), rather than "preterm" formula (Cooke 2001), did not find a statistically significant difference in weight or length at 12 - 18 months post-term. The head circumference in the enriched-formula group was statistically significantly lower than in the standard term formula group [weighted mean difference: -4.5 (95% confidence interval -9.1, -0.04) millimetres]. This meta-analysis did not demonstrate statistical heterogeneity.

Subgroup analyses of only the trial that used "preterm" formula (Cooke 2001), did not find a statistically significant difference in length or head circumference at 12 - 18 months post-term. Infants in the enriched-formula group were statistically significantly heavier than infants in the standard term formula group [mean difference: 500 (95% confidence interval 25, 974) grams].

Development (Outcome 01.05)

Neither Cooke 2001 nor Lucas 2001, nor a meta-analysis of data from both trials detected a statistically significant difference in the Bayley Scales Mental Development Index [weighted mean difference 0.23 (95% confidence interval -2.99 to 3.45)] or Psychomotor Development Index [weighted mean difference 0.55 (95% confidence interval -1.95 to 3.05)]. Lucas 2001 reported no statistically significant difference in the "number of infants considered to have either a possible or definite neurological deficit" (not defined further) at 18 months post-term. None of the included trials assessed cognitive and educational outcomes.

SECONDARY OUTCOMES:

Bone mineralisation (Outcome 01.06)

Cooke 2001 assessed body composition with dual energy x-ray absorptiometry at six months and again at 12 months post-term. There were not any statistically significant differences in the bone area, bone mineral mass, or bone mineral density measurements between the groups. In the published report, all of these data were presented in graphs and could not be extracted for estimation of mean differences. The investigators also reported that there were not any statistically significant differences in the 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. De Curtis 2002 did not find any statistically significant differences in the bone mineral content or the bone area at the end of the two months study period. Koo 2006 reported that at the end of the 12 months study period the infants who received nutrient-enriched formula had statistically significantly lower bone mass (measured using dual-energy X-ray adsorptiometry). The data were presented in graphs and could not be extracted for calculation of mean differences. Lucas 1992 assessed bone width and bone mineral content of the radius at nine months post-term. The bone width was not statistically significantly different between the groups. The bone mineral content was statistically significantly higher in the group of infants who received the nutrient-enriched formula milk: Mean difference 20.6 (95% confidence interval 7.8 to 33.4) milligrams/centimetre. Lucas 2001did not assess any measures of bone mineralisation. Litmanovitz 2004 did not find any statistically significant differences in bone strength assessed as "bone speed of sound" measured with ultrasound or in serum levels of bone specific alkaline phosphatase at six months post-term.

Feed intolerance

Only Lucas 1992 assessed this outcome. There were no statistically significant differences in the mean numbers of vomits or possets per day. None of the participating infants ceased taking a study formula because of feed intolerance. None of the three trials that reported the time of introduction of weaning foods found a statistically significant difference (Cooke 2001; Lucas 1992; Lucas 2001).

None of the trials assessed the effect of the intervention on clinical or radiological evidence of rickets, or on body mass index or blood pressure on long-term follow-up.

Sub-group analyses:

1. infants of very low birth weight (less than 1.5 kilograms) or who are very preterm at birth (less than 32 weeks): Only one trial recruited exclusively very low birth weight infants (Litmanovitz 2004). As detailed above, the investigators did not find any statistically significant difference in the weight, length, or head circumference, or in measures of bone mineralisation at six months post-term.

2. infants who remain small for gestational age (less than 10th percentile for weight) at hospital discharge: No subgroup data available.

3. infants with chronic lung disease requiring home supplemental

oxygen therapy: No subgroup data available.
4. infants fed standard term formula versus infants fed "preterm" formula: One trial (Cooke 2001)- see above.
5. infants fed standard term formula versus infants fed "post-discharge" formula: Six trials (Carver 2001; De Curtis 2002; Koo 2006; Litmanovitz 2004; Lucas 1992; Lucas 2001)- see above.

DISCUSSION

No evidence was found demonstrating that post-hospital discharge growth of preterm infants is higher in infants who receive nutrient-enriched formula milk compared to standard term formula. In fact, meta-analyses of data from two trials suggests that infants who are fed with nutrient-enriched formula have statistically significantly lower weights, lengths, and head circumferences at six months post-discharge. The clinical significance of these findings is unclear. Meta-analyses of trials that undertook longer follow-up (12 to 18 months) did not reveal any statistically significant differences in these growth parameters. Data from one trial indicated that preterm infants fed with formula milk with 80 kcal/100ml and 2.2 grams of protein/100ml ("preterm formula") weighed about 500 grams heavier at 18 months post-term. It is not yet known whether this difference persists through later childhood. The effect of this intervention on long term development is also unclear. The available data do not provide any evidence that feeding with nutrient-enriched formula milk improves neurodevelopmental outcomes when assessed at 18 months post-term. There are not yet any data on longer-term cognitive and educational outcomes.

The infants who participated in the included trials were fed ad libitum. Nutrient intake was measured in four of the trials (Carver 2001; Cooke 2001; De Curtis 2002; Lucas 1992). De Curtis 2002 and Lucas 1992 found that the volume of milk consumed during the study period was not statistically significantly different between the comparison groups. However, Carver 2001 and Cooke 2001 found that the infants fed with standard term milk consumed more milk than those fed with nutrient-enriched formula. As a consequence of this adjustment of intake, infants in the comparison groups in these trials received similar levels of calories suggesting that the primary regulation of volume of intake is determined by the energy content of the milk. The infants fed with nutrient-enriched formula milk still received more protein and minerals than infants who received standard term formula. Protein and mineral supplements are necessary to promote the accumulation of lean body and bone mass. However, it is interesting to note the findings of those trials could not be included in this review because the nutrient-enriched formula milk differed only in protein and mineral content (but not energy) from standard term formula. One trial found evidence that feeding with protein- and mineral-enriched milk was associated with higher rates of growth (Wheeler 1996), but the other two studies found no evidence of effect (Chan 1994; Cooper 1985).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that feeding preterm infants after hospital discharge with a nutrient-enriched formula milk (compared to a standard term formula) leads to a higher rates of growth or affects neurodevelopment.

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, and on later neurodevelopmental outcomes. Further large randomised controlled trials are needed to evaluate the effects of feeding preterm infants with nutrient-enriched formula milks following hospital discharge. It may be appropriate to focus research efforts on the subgroup of preterm infants who are not able to feed ad libitum following hospital discharge, and who have extra metabolic demands, for example because of growth restriction or chronic lung disease. Trials should aim to assess long-term clinically important outcomes, principally final height and body composition and neurodevelopment (including cognitive and educational outcomes).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Carver 2001

Methods	Blinding of randomisation: can't tell Blinding of intervention: yes Complete follow-up: no Blinding of outcome measurement: yes
Participants	125 preterm infants (birth weight less than 1800 grams or gestation less than 37 weeks). Infants with severe bronchopulmonary dysplasia, cardiac, respiratory, gastrointestinal ir other systemic diseases at time of discharge were not eligible to participate.
Interventions	Nutrient-enriched formula (energy content 74 kcal/100ml, protein content 1.9 grams/100ml, and calcium and phosphorus content 78 mg/100ml and 46 mg/100ml respectively) (N= 67) or standard term formula (energy content 68 kcal/100ml, protein content 1.5 grams/100ml) (N= 56). The intention was for the allocated formula to be the main milk source from hospital discharge until twelve months post-term.
Outcomes	Growth parameters at intervals until the end of the 12 months study period.
Notes	Setting: Multi-centre, six perinatal centres in North America. Loss to follow up (study exit). Infants exited the study early (and did not have growth parameters measured) for a variety of reasons including study non-compliance (not defined or described), gastro-intestinal upset, and "illness unrelated to the study feedings" (not defined or described). 31 of 67 in post-discharge formula group, and 26 of 56 in standard term formula group left the study early (plus two other infants who were randomised but did not take part in the study). The total loss of follow up is 59 of 125 (47%) but not clear at which time points these infants left the trial.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cooke 2001

Methods	Blinding of randomisation: can't tell Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: yes

Cooke 2001 (*Continued)*

Participants	103 preterm infants (birth weight less than 1750 grams or gestation less than 35 weeks). Only infants who were "growing normally" (rate of weight gain more than 25 grams/kg/day) at time of discharge were eligible to participate.
Interventions	Nutrient-enriched formula (energy content 80 kcal/100ml, protein content 2.2 grams/100ml, and calcium and phosphorus content 108 mg/100ml and 54 mg/100ml respectively) (N= 49) or a standard term formula (energy content 66 kcal/100ml, protein content 1.4 grams/100ml) (N= 54) from hospital discharge until six months post term.
Outcomes	Anthropometric and developmental parameters (including Bayley Scales of Infant Development II) and measures of bone mineralisation.
Notes	Setting: Royal Victoria Hospital, Newcastle upon Tyne, UK. This trial included a third randomised group of infants (N= 26) allocated to receive "preterm" formula from the time of hospital discharge until they reach "term", and then standard term formula from that point until six months post-term. Cooke 2001 reported growth data for boys and girls separately. We combined the data for inclusion in this review.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

De Curtis 2002

Methods	Blinding of randomisation: can't tell Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: yes
Participants	33 formula milk-fed preterm infants (birth weight less than 1750 grams or gestation less than 35 weeks).
Interventions	Nutrient-enriched formula (energy content 74 kcal/100ml, protein content 1.8 grams/100ml, and calcium and phosphorus content 80 mg/100ml and 40 mg/100ml respectively) (N= 16) or standard term formula (energy content 66 kcal/100ml, protein content 1.4 grams/100ml) (N= 17) from hospital discharge until two months post-term.
Outcomes	Growth parameters and bone mineralisation measured using dual energy x-ray absorptiometry at the end of the 2 months study period.
Notes	Setting: Department of Pediatrics, University of Liege, Belgium.

De Curtis 2002 (*Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Koo 2006

Methods	Blinding of randomisation: no Blinding of intervention: yes Complete follow-up: no Blinding of outcome measurement: yes
Participants	89 preterm infants ready for hospital discharge (gestational age at birth less than 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/100ml, protein content 1.9 grams/100ml, and calcium and phosphorus content 78 mg/100ml and 46 mg/100ml respectively) (N= 44) or standard term formula (energy content 67 kcal/100ml, protein content 1.5 grams/100ml) (N= 45). The intention was for the allocated formula to be fed ad libitum until twelve months efter discharge.
Outcomes	Growth parameters and bone mineral content at intervals until the end of the 12 months study period.
Notes	Setting: Department of Pediatrics, Wayne State University and Hutzel Hospital, Detroit, USA.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Litmanovitz 2004

Methods	Blinding of randomisation: can't tell Blinding of intervention: can't tell Complete follow-up: yes Blinding of outcome measurement: can't tell
Participants	20 healthy very low birth weight infants at hospital discharge.

Interventions	Nutrient-enriched formula (energy content 74 kcal/100ml, protein content 1.9 grams/100ml (N= 10) or a standard term formula (energy content 67 kcal/100ml, protein content 1.5 grams/100ml) (N= 10) following hospital discharge. The formulas were intended to provide the sole milk intake up to a post-term age of six months.
Outcomes	Weight, length, head circumference, and measures of bone mineralisation at term and at six months post-term.
Notes	Setting: Meir General Hospital, Kfar-saba, Israel.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lucas 1992

Methods	Blinding of randomisation: can't tell Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: can't tell
Participants	32 exclusively bottle-fed preterm infants, birth weight less than 1850 grams, and weight less than 3000 grams at hospital discharge.
Interventions	Nutrient-enriched formula (energy content 72 kcal/100ml, protein content 1.85 grams/100ml, and calcium and phosphorus content 70 mg/100ml and 35 mg/100ml respectively) (N= 16)or a standard term formula (energy content 68 kcal/100ml, protein content 1.4 grams/100ml) (N=15) following hospital discharge. The formulas were intended to provide the sole milk intake up to a post-term age of nine months.
Outcomes	Measures of growth (weight, crown-heel length and head circumference), feed tolerance, and bone mineralisation during the trial period.
Notes	Setting: Department of Paediatrics, Rosie Maternity Hospital, Cambridge. One infant who was randomised to the standard term formula group was transferred to another hospital prior to the planned hospital discharge and could not be included in any follow up assessments.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lucas 2001

Methods	Blinding of randomisation: yes (sealed opaque envelopes) Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: yes
Participants	229 formula milk-fed preterm infants, birth weight less than 1750 grams, and weight less than 3000 grams at hospital discharge.
Interventions	Nutrient-enriched formula (energy content 72 kcal/100ml, protein content 1.85 grams/100ml, and calcium and phosphorus content 70 mg/100ml and 35 mg/100ml respectively) (N= 113) or standard term formula (energy content 68 kcal/100ml, protein content 1.5 grams/100ml) (N= 116) from hospital-discharge until nine months post-term.
Outcomes	Growth parameters up to 18 months post-term, and neuro-development (Bayley Scales) at 18 months post-term.
Notes	Setting: Five neonatal centres in the UK. 1993-5. Growth outcomes assessed for all participating infants, developmental assessments available for 184 (of 229) recruited infants.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Agosti 2003	The “control” formula milk was protein-enriched (1.7 grams/ 100ml).
Bhatia 1991	Both of the formula milks had protein concentrations of less than 1.6 grams/ 100ml.
Brunton 1998	Both of the formula milks were calorie-enriched.
Chan 1994	Neither of the formula milks were calorie-enriched.
Cooper 1985	Neither of the formula milks were calorie-enriched.
Wheeler 1996	Neither of the formula milks were calorie-enriched.

DATA AND ANALYSES

Comparison 1. Nutrient-enriched 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 (grams/ kilogram/day)	1	33	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Linear growth (millimetres/week)	1	33	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Head circumference (millimetres/week)	1	33	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Growth parameters at 6 months post -term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Weight at 6 months post-term (grams)	2	87	Mean Difference (IV, Fixed, 95% CI)	-601.07 [-1027.98, -174.15]
2.2 Crown-heel length at 6 months post-term (millimetres)	2	87	Mean Difference (IV, Fixed, 95% CI)	-18.79 [-30.00, -7.58]
2.3 Head circumference at 6 months post-term (millimetres)	2	87	Mean Difference (IV, Fixed, 95% CI)	-10.20 [-18.02, -2.38]
3 Growth parameters at 9 months post -term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Weight at 9 months post term (grams)	2	296	Mean Difference (IV, Fixed, 95% CI)	152.54 [-90.42, 395.49]
3.2 Crown-heel length at 9 months post-term (millimetres)	2	296	Mean Difference (IV, Fixed, 95% CI)	5.08 [-1.58, 11.74]
3.3 Head circumference at 9 months post-term (millimetres)	2	296	Mean Difference (IV, Fixed, 95% CI)	-1.88 [-5.67, 1.90]
4 Growth parameters at 12-18 months post -term	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Weight at 12-18 months post term (grams)	3	362	Mean Difference (IV, Fixed, 95% CI)	73.51 [-182.31, 329.32]
4.2 Crown-heel length at 12-18 months post-term (millimetres)	3	362	Mean Difference (IV, Fixed, 95% CI)	4.94 [-1.37, 11.24]
4.3 Head circumference at 12-18 months post-term (millimetres)	3	362	Mean Difference (IV, Fixed, 95% CI)	-1.23 [-4.88, 2.41]
5 Development	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Bayley Scales of Infant Development II: Mental Development Index	2	299	Mean Difference (IV, Fixed, 95% CI)	0.23 [-2.99, 3.45]
5.2 Bayley Scales of Infant Development II: Psychomotor Development Index	2	299	Mean Difference (IV, Fixed, 95% CI)	0.55 [-1.95, 3.05]
6 Bone mineralisation	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

6.1 Bone area at 2 months post-term (centimetres squared)	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" assessed with ultrasound at 6 months post-term (millimetres/ second)	1	20	Mean Difference (IV, Fixed, 95% CI)	45.0 [-18.48, 108.48]
6.4 Bone specific serum alkaline phosphatase at six months post-term (units/litre)	1	20	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-42.01, 24.01]
6.5 Bone width at 9 months post-term (centimetres)	1	31	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.11]
6.6 Bone mineral content at 9 months post-term (milligrams/ centimetre)	1	31	Mean Difference (IV, Fixed, 95% CI)	20.60 [7.78, 33.42]

Comparison 2. "Post-discharge" nutrient-enriched formula versus standard term formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth parameters at 12-18 months post -term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Weight at 12-18 months post term (grams)	2	259	Mean Difference (IV, Fixed, 95% CI)	-101.64 [-405.48, 202.19]
1.2 Crown-heel length at 12-18 months post-term (millimetres)	2	259	Mean Difference (IV, Fixed, 95% CI)	2.13 [-5.49, 9.76]
1.3 Head circumference at 12-18 months post-term (millimetres)	2	259	Mean Difference (IV, Fixed, 95% CI)	-4.55 [-9.06, -0.04]
2 Development	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Bayley Scales of Infant Development II: Mental Development Index	1	196	Mean Difference (IV, Fixed, 95% CI)	0.90 [-3.11, 4.91]
2.2 Bayley Scales of Infant Development II: Psychomotor Development Index	1	196	Mean Difference (IV, Fixed, 95% CI)	2.70 [-1.16, 6.56]

Comparison 3. "Preterm" nutrient-enriched formula versus standard term formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth parameters at 12-18 months post -term	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Weight at 12-18 months post term (grams)	1	103	Mean Difference (IV, Fixed, 95% CI)	500.00 [25.87, 974.13]
1.2 Crown-heel length at 12-18 months post-term (millimetres)	1	103	Mean Difference (IV, Fixed, 95% CI)	11.0 [-0.21, 22.21]
1.3 Head circumference at 12-18 months post-term (millimetres)	1	103	Mean Difference (IV, Fixed, 95% CI)	5.0 [-1.18, 11.18]
2 Development	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Bayley Scales of Infant Development II: Mental Development Index	1	103	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-6.41, 4.41]
2.2 Bayley Scales of Infant Development II: Psychomotor Development Index	1	103	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-4.30, 2.30]

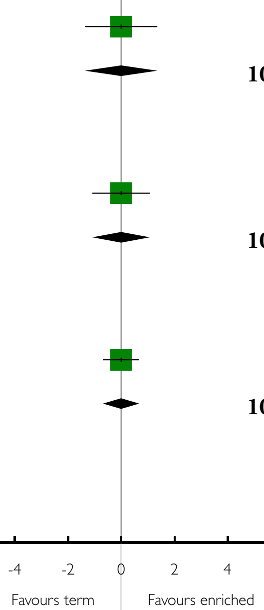
Analysis 1.1. Comparison 1 Nutrient-enriched formula versus standard term formula, Outcome 1 Growth rates during trial period.

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

Comparison: 1 Nutrient-enriched formula versus standard term formula

Outcome: 1 Growth rates during trial period

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Weight gain (grams/kilogram/day)							
De Curtis 2002	16	10 (2)	17	10 (2)		100.0 %	0.0 [-1.37, 1.37]
Subtotal (95% CI)	**16**		**17**			**100.0 %**	**0.0 [-1.37, 1.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 Linear growth (millimetres/week)							
De Curtis 2002	16	10 (1)	17	10 (2)		100.0 %	0.0 [-1.07, 1.07]
Subtotal (95% CI)	**16**		**17**			**100.0 %**	**0.0 [-1.07, 1.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
3 Head circumference (millimetres/week)							
De Curtis 2002	16	6 (1)	17	6 (1)		100.0 %	0.0 [-0.68, 0.68]
Subtotal (95% CI)	**16**		**17**			**100.0 %**	**0.0 [-0.68, 0.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Test for subgroup differences: Chi^2 = 0.0, df = 2 (P = 1.00), I^2 =0.0%							



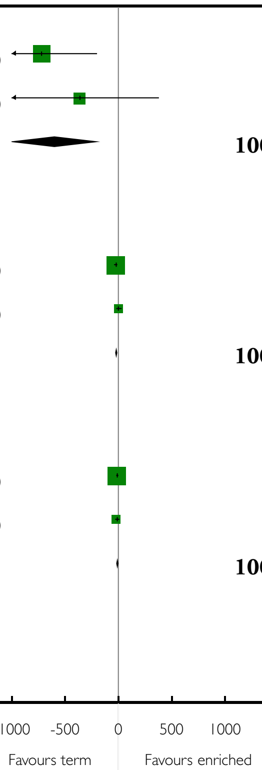
Analysis 1.2. Comparison 1 Nutrient-enriched formula versus standard term formula, Outcome 2 Growth parameters at 6 months post -term.

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

Comparison: 1 Nutrient-enriched formula versus standard term formula

Outcome: 2 Growth parameters at 6 months post -term

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Weight at 6 months post-term (grams)							
Koo 2006	31	6492 (1024)	36	7210 (1156)		66.9 %	-718.00 [-1240.05, -195.95]
Litmanovitz 2004	10	6948 (975)	10	7313 (694)		33.1 %	-365.00 [-1106.75, 376.75]
Subtotal (95% CI)	**41**		**46**			**100.0 %**	**-601.07 [-1027.98, -174.15]**
Heterogeneity: $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.76 (P = 0.0058)							
2 Crown-heel length at 6 months post-term (millimetres)							
Koo 2006	31	612 (24.5)	36	636 (27.6)		80.7 %	-24.00 [-36.48, -11.52]
Litmanovitz 2004	10	659 (36)	10	656 (20)		19.3 %	3.00 [-22.52, 28.52]
Subtotal (95% CI)	**41**		**46**			**100.0 %**	**-18.79 [-30.00, -7.58]**
Heterogeneity: $Chi^2 = 3.47$, df = 1 (P = 0.06); $I^2 = 71\%$							
Test for overall effect: Z = 3.29 (P = 0.0010)							
3 Head circumference at 6 months post-term (millimetres)							
Koo 2006	31	419 (17.8)	36	429 (18.6)		80.3 %	-10.00 [-18.73, -1.27]
Litmanovitz 2004	10	431 (18)	10	442 (22)		19.7 %	-11.00 [-28.62, 6.62]
Subtotal (95% CI)	**41**		**46**			**100.0 %**	**-10.20 [-18.02, -2.38]**
Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.56 (P = 0.011)							
Test for subgroup differences: $Chi^2 = 8.81$, df = 2 (P = 0.01), $I^2 = 77\%$							



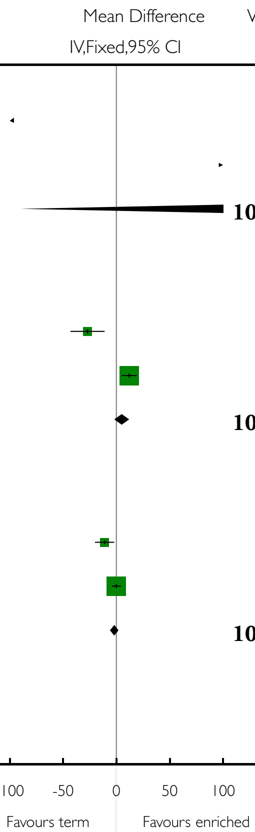
Analysis 1.3. Comparison 1 Nutrient-enriched formula versus standard term formula, Outcome 3 Growth parameters at 9 months post -term.

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

Comparison: 1 Nutrient-enriched formula versus standard term formula

Outcome: 3 Growth parameters at 9 months post -term

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Weight at 9 months post term (grams)						
Koo 2006	31	7765 (1120)	36	8629 (1297)	17.6 %	-864.00 [-1442.75, -285.25]
Lucas 2001	113	8360 (1100)	116	7990 (960)	82.4 %	370.00 [102.32, 637.68]
Subtotal (95% CI)	**144**		**152**		**100.0 %**	**152.54 [-90.42, 395.49]**
Heterogeneity: $Chi^2 = 14.39$, df = 1 (P = 0.00015); I^2 =93%						
Test for overall effect: Z = 1.23 (P = 0.22)						
2 Crown-heel length at 9 months post-term (millimetres)						
Koo 2006	31	668 (30.6)	36	695 (35.4)	17.7 %	-27.00 [-42.80, -11.20]
Lucas 2001	113	709 (32)	116	697 (24)	82.3 %	12.00 [4.66, 19.34]
Subtotal (95% CI)	**144**		**152**		**100.0 %**	**5.08 [-1.58, 11.74]**
Heterogeneity: $Chi^2 = 19.24$, df = 1 (P = 0.00001); I^2 =95%						
Test for overall effect: Z = 1.50 (P = 0.13)						
3 Head circumference at 9 months post-term (millimetres)						
Koo 2006	31	439 (18.9)	36	450 (19.2)	17.1 %	-11.00 [-20.14, -1.86]
Lucas 2001	113	456 (17)	116	456 (15)	82.9 %	0.0 [-4.16, 4.16]
Subtotal (95% CI)	**144**		**152**		**100.0 %**	**-1.88 [-5.67, 1.90]**
Heterogeneity: $Chi^2 = 4.61$, df = 1 (P = 0.03); I^2 =78%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: $Chi^2 = 4.69$, df = 2 (P = 0.10), I^2 =57%						



Analysis 1.4. Comparison 1 Nutrient-enriched formula versus standard term formula, Outcome 4 Growth parameters at 12-18 months post -term.

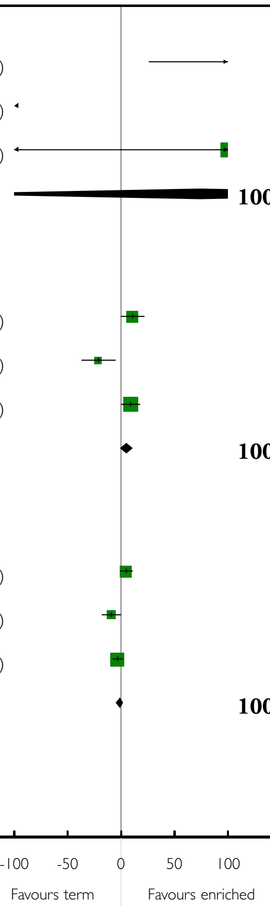
Review: Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge

Comparison: 1 Nutrient-enriched formula versus standard term formula

Outcome: 4 Growth parameters at 12-18 months post -term

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Weight at 12-18 months post term (grams)						
Cooke 2001	49	10400 (1400)	54	9900 (1000)	29.1 %	500.00 [25.87, 974.13]
Koo 2006	31	8562 (1300)	36	9328 (1324)	16.5 %	-766.00 [-1395.66, -136.34]
Lucas 2001	96	10200 (1280)	96	10100 (1170)	54.4 %	100.00 [-246.90, 446.90]
Subtotal (95% CI)	**176**		**186**		**100.0 %**	**73.51 [-182.31, 329.32]**
Heterogeneity: $Chi^2 = 9.96$, df = 2 (P = 0.01); I^2 =80%						
Test for overall effect: Z = 0.56 (P = 0.57)						
2 Crown-heel length at 12-18 months post-term (millimetres)						
Cooke 2001	49	801 (29)	54	790 (29)	31.6 %	11.00 [-0.21, 22.21]
Koo 2006	31	714 (32.3)	36	735 (34.2)	15.7 %	-21.00 [-36.94, -5.06]
Lucas 2001	96	806 (34)	96	797 (27)	52.7 %	9.00 [0.32, 17.68]
Subtotal (95% CI)	**176**		**186**		**100.0 %**	**4.94 [-1.37, 11.24]**
Heterogeneity: $Chi^2 = 12.13$, df = 2 (P = 0.002); I^2 =84%						
Test for overall effect: Z = 1.53 (P = 0.12)						
3 Head circumference at 12-18 months post-term (millimetres)						
Cooke 2001	49	485 (15)	54	480 (17)	34.7 %	5.00 [-1.18, 11.18]
Koo 2006	31	451 (18)	36	460 (19)	16.9 %	-9.00 [-17.87, -0.13]
Lucas 2001	96	476 (18)	96	479 (19)	48.4 %	-3.00 [-8.24, 2.24]
Subtotal (95% CI)	**176**		**186**		**100.0 %**	**-1.23 [-4.88, 2.41]**
Heterogeneity: $Chi^2 = 7.29$, df = 2 (P = 0.03); I^2 =73%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: $Chi^2 = 3.07$, df = 2 (P = 0.22), I^2 =35%						

Mean Difference IV,Fixed,95% CI



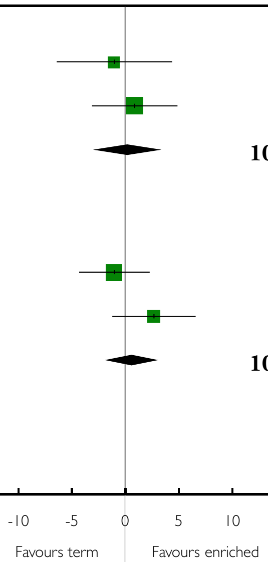
Analysis 1.5. Comparison 1 Nutrient-enriched formula versus standard term formula, Outcome 5 Development.

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

Comparison: 1 Nutrient-enriched formula versus standard term formula

Outcome: 5 Development

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bayley Scales of Infant Development II: Mental Development Index							
Cooke 2001	49	102 (14)	54	103 (14)		35.4 %	-1.00 [-6.41, 4.41]
Lucas 2001	98	92.3 (14.7)	98	91.4 (13.9)		64.6 %	0.90 [-3.11, 4.91]
Subtotal (95% CI)	**147**		**152**			**100.0 %**	**0.23 [-2.99, 3.45]**
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² =0.0%							
Test for overall effect: Z = 0.14 (P = 0.89)							
2 Bayley Scales of Infant Development II: Psychomotor Development Index							
Cooke 2001	49	102 (8)	54	103 (9)		58.0 %	-1.00 [-4.28, 2.28]
Lucas 2001	98	91.7 (12.7)	98	89 (14.8)		42.0 %	2.70 [-1.16, 6.56]
Subtotal (95% CI)	**147**		**152**			**100.0 %**	**0.55 [-1.95, 3.05]**
Heterogeneity: Chi² = 2.05, df = 1 (P = 0.15); I² =51%							
Test for overall effect: Z = 0.43 (P = 0.66)							
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² =0.0%							



Analysis 1.6. Comparison 1 Nutrient-enriched formula versus standard term formula, Outcome 6 Bone mineralisation.

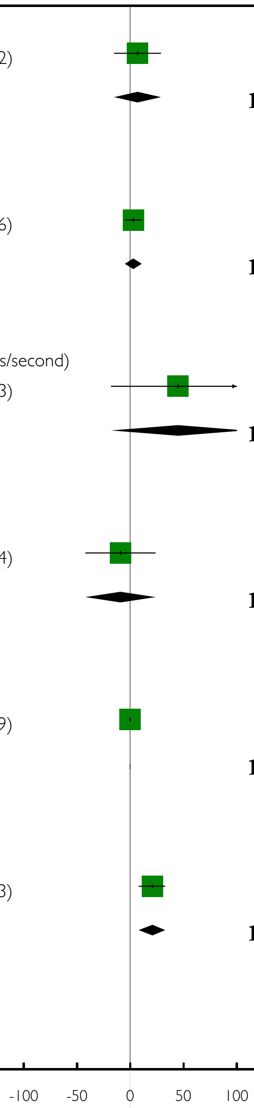
Review: Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge

Comparison: 1 Nutrient-enriched formula versus standard term formula

Outcome: 6 Bone mineralisation

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Bone area at 2 months post-term (centimetres squared)						
De Curtis 2002	16	351 (21)	17	344 (42)	100.0 %	7.00 [-15.46, 29.46]
Subtotal (95% CI)	**16**		**17**		**100.0 %**	**7.00 [-15.46, 29.46]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2 Bone mineral content at 2 months post-term (grams)						
De Curtis 2002	16	68.2 (10.6)	17	65 (12.6)	100.0 %	3.20 [-4.73, 11.13]
Subtotal (95% CI)	**16**		**17**		**100.0 %**	**3.20 [-4.73, 11.13]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
3 Bone "speed of sound" assessed with ultrasound at 6 months post-term (millimetres/second)						
Litmanovitz 2004	10	3032 (60)	10	2987 (83)	100.0 %	45.00 [-18.48, 108.48]
Subtotal (95% CI)	**10**		**10**		**100.0 %**	**45.00 [-18.48, 108.48]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.39 (P = 0.16)						
4 Bone specific serum alkaline phosphatase at six months post-term (units/litre)						
Litmanovitz 2004	10	125 (41)	10	134 (34)	100.0 %	-9.00 [-42.01, 24.01]
Subtotal (95% CI)	**10**		**10**		**100.0 %**	**-9.00 [-42.01, 24.01]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
5 Bone width at 9 months post-term (centimetres)						
Lucas 1992	16	0.67 (0.09)	15	0.62 (0.09)	100.0 %	0.05 [-0.01, 0.11]
Subtotal (95% CI)	**16**		**15**		**100.0 %**	**0.05 [-0.01, 0.11]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
6 Bone mineral content at 9 months post-term (milligrams/centimetre)						
Lucas 1992	16	115.3 (21.6)	15	94.7 (14.3)	100.0 %	20.60 [7.78, 33.42]
Subtotal (95% CI)	**16**		**15**		**100.0 %**	**20.60 [7.78, 33.42]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.15 (P = 0.0016)						
Test for subgroup differences: Chi^2 = 13.06, df = 5 (P = 0.02), I^2 =62%						

Mean Difference IV,Fixed,95% CI



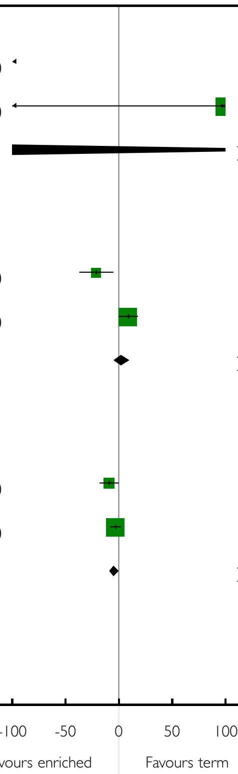
Analysis 2.1. Comparison 2 "Post-discharge" nutrient-enriched formula versus standard term formula, Outcome 1 Growth parameters at 12-18 months post -term.

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

Comparison: 2 "Post-discharge" nutrient-enriched formula versus standard term formula

Outcome: 1 Growth parameters at 12-18 months post -term

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Weight at 12-18 months post term (grams)						
Koo 2006	31	8562 (1300)	36	9328 (1324)	23.3 %	-766.00 [-1395.66, -136.34]
Lucas 2001	96	10200 (1280)	96	10100 (1170)	76.7 %	100.00 [-246.90, 446.90]
Subtotal (95% CI)	**127**		**132**		**100.0 %**	**-101.64 [-405.48, 202.19]**
Heterogeneity: Chi² = 5.57, df = 1 (P = 0.02); I² =82%						
Test for overall effect: Z = 0.66 (P = 0.51)						
2 Crown-heel length at 12-18 months post-term (millimetres)						
Koo 2006	31	714 (32.3)	36	735 (34.2)	22.9 %	-21.00 [-36.94, -5.06]
Lucas 2001	96	806 (34)	96	797 (27)	77.1 %	9.00 [0.32, 17.68]
Subtotal (95% CI)	**127**		**132**		**100.0 %**	**2.13 [-5.49, 9.76]**
Heterogeneity: Chi² = 10.49, df = 1 (P = 0.001); I² =90%						
Test for overall effect: Z = 0.55 (P = 0.58)						
3 Head circumference at 12-18 months post-term (millimetres)						
Koo 2006	31	451 (18)	36	460 (19)	25.8 %	-9.00 [-17.87, -0.13]
Lucas 2001	96	476 (18)	96	479 (19)	74.2 %	-3.00 [-8.24, 2.24]
Subtotal (95% CI)	**127**		**132**		**100.0 %**	**-4.55 [-9.06, -0.04]**
Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² =23%						
Test for overall effect: Z = 1.98 (P = 0.048)						
Test for subgroup differences: Chi² = 2.59, df = 2 (P = 0.27), I² =23%						



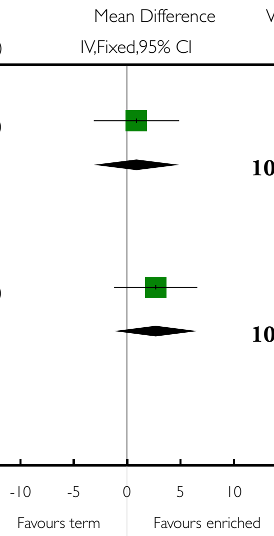
Analysis 2.2. Comparison 2 "Post-discharge" nutrient-enriched formula versus standard term formula, Outcome 2 Development.

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

Comparison: 2 "Post-discharge" nutrient-enriched formula versus standard term formula

Outcome: 2 Development

Study or subgroup	Enriched formula N	Mean(SD)	Term formula N	Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Bayley Scales of Infant Development II: Mental Development Index						
Lucas 2001	98	92.3 (14.7)	98	91.4 (13.9)	100.0 %	0.90 [-3.11, 4.91]
Subtotal (95% CI)	**98**		**98**		**100.0 %**	**0.90 [-3.11, 4.91]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
2 Bayley Scales of Infant Development II: Psychomotor Development Index						
Lucas 2001	98	91.7 (12.7)	98	89 (14.8)	100.0 %	2.70 [-1.16, 6.56]
Subtotal (95% CI)	**98**		**98**		**100.0 %**	**2.70 [-1.16, 6.56]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: $Chi^2 = 0.40$, df = 1 (P = 0.53), $I^2 = 0.0\%$						



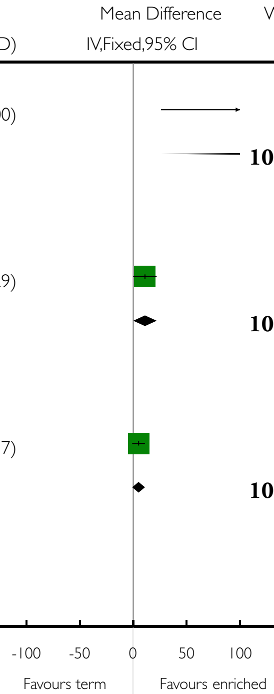
Analysis 3.1. Comparison 3 "Preterm" nutrient-enriched formula versus standard term formula, Outcome 1 Growth parameters at 12-18 months post -term.

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

Comparison: 3 "Preterm" nutrient-enriched formula versus standard term formula

Outcome: 1 Growth parameters at 12-18 months post -term

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
1 Weight at 12-18 months post term (grams)						
Cooke 2001	49	10400 (1400)	54	9900 (1000)	100.0 %	500.00 [25.87, 974.13]
Subtotal (95% CI)	**49**		**54**		**100.0 %**	**500.00 [25.87, 974.13]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.07 (P = 0.039)						
2 Crown-heel length at 12-18 months post-term (millimetres)						
Cooke 2001	49	801 (29)	54	790 (29)	100.0 %	11.00 [-0.21, 22.21]
Subtotal (95% CI)	**49**		**54**		**100.0 %**	**11.00 [-0.21, 22.21]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.92 (P = 0.055)						
3 Head circumference at 12-18 months post-term (millimetres)						
Cooke 2001	49	485 (15)	54	480 (17)	100.0 %	5.00 [-1.18, 11.18]
Subtotal (95% CI)	**49**		**54**		**100.0 %**	**5.00 [-1.18, 11.18]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi^2 = 5.01, df = 2 (P = 0.08), I^2 =60%						



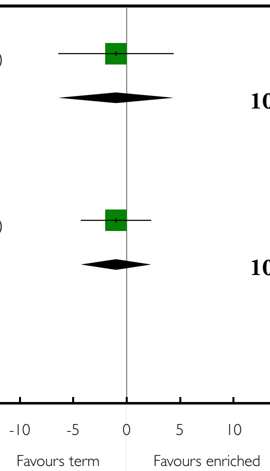
Analysis 3.2. Comparison 3 "Preterm" nutrient-enriched formula versus standard term formula, Outcome 2 Development.

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

Comparison: 3 "Preterm" nutrient-enriched formula versus standard term formula

Outcome: 2 Development

Study or subgroup	Enriched formula N	Enriched formula Mean(SD)	Term formula N	Term formula Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bayley Scales of Infant Development II: Mental Development Index							
Cooke 2001	49	102 (14)	54	103 (14)		100.0 %	-1.00 [-6.41, 4.41]
Subtotal (95% CI)	**49**		**54**			**100.0 %**	**-1.00 [-6.41, 4.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.36 (P = 0.72)							
2 Bayley Scales of Infant Development II: Psychomotor Development Index							
Cooke 2001	54	102 (8)	49	103 (9)		100.0 %	-1.00 [-4.30, 2.30]
Subtotal (95% CI)	**54**		**49**			**100.0 %**	**-1.00 [-4.30, 2.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.59 (P = 0.55)							
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%							



WHAT'S NEW

Last assessed as up-to-date: 24 June 2007.

28 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 2, 2005

25 June 2007	New citation required but conclusions have not changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

William McGuire and Tom Fahey developed the protocol for the review. Ginny Henderson and William McGuire undertook the literature search, appraised the reports (independently), extracted the data (independently), and completed the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- ANU Medical School, Canberra, Australia.
- Royal College of Surgeons in Ireland, Ireland.
- Griffith University, Queensland, Australia.

External sources

- Tenovus, Scotland, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans