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Formula versus donor breast milk for feeding preterm or low birth weight infants (Review)

Quigley M, Embleton ND, McGuire W

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[Intervention Review]

Formula versus donor breast milk for feeding preterm or low birth weight infants

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ABSTRACT

Background

When sufficient maternal breast milk is not available, alternative forms of enteral nutrition for preterm or low birth weight (LBW) infants are donor breast milk or artificial formula. Donor breast milk may retain some of the non-nutritive benefits of maternal breast milk for preterm or LBW infants. However, feeding with artificial formula may ensure more consistent delivery of greater amounts of nutrients. Uncertainty exists about the balance of risks and benefits of feeding formula versus donor breast milk for preterm or LBW infants.

Objectives

To determine the effect of feeding with formula compared with donor breast milk on growth and development in preterm or low birth weight (LBW) infants.

Search methods

We used the Cochrane Neonatal search strategy, including electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 5), Ovid MEDLINE, Embase, and the Cumulative Index to Nursing and Allied Health Literature (3 May 2019), as well as conference proceedings, previous reviews, and clinical trials.

Selection criteria

Randomised or quasi-randomised controlled trials (RCTs) comparing feeding with formula versus donor breast milk in preterm or LBW infants.

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 (RRs) and risk differences (RDs) 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 in subgroup analyses. We assessed the certainty of evidence for the main comparison at the outcome level using GRADE methods.

Main results

Twelve trials with a total of 1879 infants fulfilled the inclusion criteria. Four trials compared standard term formula versus donor breast milk and eight compared nutrient-enriched preterm formula versus donor breast milk. Only the five most recent trials used nutrient-fortified

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donor breast milk. The trials contain various weaknesses in methodological quality, specifically concerns about allocation concealment in four trials and lack of blinding in most of the trials. Most of the included trials were funded by companies that made the study formula.

Formula-fed infants had higher in-hospital rates of weight gain (mean difference (MD) 2.51, 95% confidence interval (CI) 1.93 to 3.08 g/kg/day), linear growth (MD 1.21, 95% CI 0.77 to 1.65 mm/week) and head growth (MD 0.85, 95% CI 0.47 to 1.23 mm/week). These meta-analyses contained high levels of heterogeneity. We did not find evidence of an effect on long-term growth or neurodevelopment. Formula feeding increased the risk of necrotising enterocolitis (typical risk ratio (RR) 1.87, 95% CI 1.23 to 2.85; risk difference (RD) 0.03, 95% CI 0.01 to 0.05; number needed to treat for an additional harmful outcome (NNTH) 33, 95% CI 20 to 100; 9 studies, 1675 infants).

The GRADE certainty of evidence was moderate for rates of weight gain, linear growth, and head growth (downgraded for high levels of heterogeneity) and was moderate for neurodevelopmental disability, all-cause mortality, and necrotising enterocolitis (downgraded for imprecision).

Authors' conclusions

In preterm and LBW infants, moderate-certainty evidence indicates that feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or as a sole diet, results in higher rates of weight gain, linear growth, and head growth and a higher risk of developing necrotising enterocolitis. The trial data do not show an effect on all-cause mortality, or on long-term growth or neurodevelopment.

PLAIN LANGUAGE SUMMARY

Formula versus donor breast milk for feeding preterm or low birth weight infants

Review question

When a mother's own breast milk is not available, does feeding preterm or low birth weight infants with formula rather than donor breast milk affect digestion, growth and the risk of severe bowel problems?

Background

Preterm infants often find artificial formula more difficult to digest than human milk, and concerns exist that formula could increase the risk of severe bowel problems. If preterm infants are fed with donor breast milk (when a mother's own breast milk is insufficient or unavailable), rather than an artificial formula, this might reduce the risk of these problems. Donor breast milk, however, is more expensive than many formulas, and may not contain sufficient amounts of key nutrients to ensure optimal growth for preterm or low birth weight infants. Given these concerns, we have reviewed all of the available evidence from clinical trials that compared formula versus donor breast milk for feeding preterm or low birth weight infants.

Study characteristics

We found 12 completed trials (involving 1871 infants). Most trials, particularly those trials conducted more recently, used reliable methods. Evidence is up to date as of 3 May 2019.

Key results

The combined analysis of data from these trials shows that feeding with formula increases rates of growth during the hospital stay, but is associated with a higher risk of developing the severe gut disorder called 'necrotising enterocolitis'. There is no evidence of an effect on survival or longer-term growth and development.

Conclusions

The currently available evidence suggests that feeding preterm infants with artificial formula (rather than donor breast milk when mother's own breast milk is not available) is associated with faster rates of growth, but with a near-doubling of the risk of developing necrotising enterocolitis. Further, larger trials could provide stronger and more precise evidence to help clinicians and families make informed choices about this issue. Currently, four such trials (involving more than 1100 infants) are ongoing internationally, and we plan to include the data from these trials in this review when these become available.

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Summary of findings for the main comparison. Formula versus donor breast milk for feeding preterm or low birth weight infants

Formula (term or preterm) compared to donor breast milk (unfortified or fortified) for feeding preterm or low birth weight infants						
Patient or population: preterm or low birth weight infants **Setting: neonatal unit** **Intervention: formula (term or preterm)** **Comparison: donor breast milk (unfortified of fortified)**						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with donated breast milk (unfortified or fortified)	**Risk with formula (term or preterm)**				
Weight gain (g/kg/day)	-	MD 2.51 higher (1.93 higher to 3.08 higher)	-	1028 (9 studies)	Moderate[a]	I^2 = 90%
Linear growth (crown-heel length mm/week)	-	MD 1.21 higher (0.77 higher to 1.65 higher)	-	820 (8 studies)	Moderate[a]	I^2 = 68%
Head growth (mm/week)	-	MD 0.85 higher (0.47 higher to 1.23 higher)	-	894 (8 studies)	Moderate[a]	I^2 = 74%
Neurodevelopmental disability	Study population		RR 1.21 (0.62 to 2.35)	400 (2 studies)	Moderate[b]	
	73 per 1000	88 per 1000 (45 to 171)				
All-cause mortality	Study population		RR 1.1 (0.8 to 1.5)	1527 (7 studies)	Moderate[b]	
	86 per 1000	94 per 1000 (69 to 128)				
Necrotising enterocolitis	Study population		RR 1.87 (1.23 to 2.85)	1675 (9 studies)	Moderate[b]	
	36 per 1000	67 per 1000 (44 to 102)				

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*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

[a]Downgraded one level for heterogeneity.
[b]Downgraded one level for imprecision.

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

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BACKGROUND

Maternal breast milk is the recommended form of enteral nutrition for preterm or low birth weight (LBW) infants (AAP 2012). Breast milk contains non-nutrient factors including immunoglobulins and lactoferrin that may promote intestinal adaptation and maturation, improve enteral feed tolerance, and protect against infective and inflammatory disorders (Agostoni 2010; Arslanoglu 2013).

When sufficient maternal breast milk is not available, the two common alternatives available for feeding preterm or LBW infants are artificial formula and donor breast milk (donated by other lactating women). These may be given either as the sole form of enteral feeding or as a supplement to maternal breast milk (Klingenberg 2012).

Description of the condition

Providing appropriate nutrition for preterm or LBW infants is a critical component of neonatal care. Early enteral nutrition strategies may have a substantial impact on clinically important outcomes, such as necrotising enterocolitis and invasive infection. These infectious and inflammatory complications may increase the risk of mortality and other morbidities and adversely affect long-term growth and neurodevelopmental outcomes.

Description of the intervention

A variety of artificial formulas (usually adapted from cow's milk) are available. These vary in energy, protein and mineral content but can, broadly, be considered as:

- standard 'term' formula, designed for term infants based on the composition of mature breast milk; the typical energy content is approximately between 67 kCal/100 mL to 70 kCal/100 mL;
- nutrient-enriched 'preterm' formula, designed to provide nutrient intakes to match intrauterine accretion rates (Tsang 1993); these are energy-enriched (typically up to approximately 80 kCal/100 mL) and variably protein- and mineral-enriched (Fewtrell 1999).

The comparison arm for the intervention is donor breast milk. Expressed breast milk from donor mothers, usually mothers who have delivered at term, generally has a lower content of energy and protein than term formula milk (Gross 1980; Gross 1981). The macronutrient content of donor breast milk is not compromised substantially by modern pasteurisation methods but levels of immunoactive components might be reduced (Peila 2016; Castro 2019). Donor human milk also varies with regard to fat, energy and protein content, depending upon the stage of lactation at which it is collected. Milk expressed from the donor's lactating breast usually has a higher energy and protein content than that collected from the contralateral breast ('drip' breast milk) (Lucas 1978).

How the intervention might work

There is concern that the nutritional requirements of preterm or LBW infants, who are born with relatively impoverished nutrient reserves and are subject to additional metabolic stresses compared with term infants, may not be fully met by enteral feeding with donor breast milk (Hay 1994; Schanler 1995). These deficiencies may have adverse consequences for growth and development. However, a major putative benefit of donor breast milk is that the delivery of immunoprotective and growth factors to the immature gut mucosa may prevent serious adverse outcomes, including necrotising enterocolitis and invasive infection (Lucas 1990; Beeby 1992).

Why it is important to do this review

Given the potential for the type of enteral nutrition to affect important outcomes for preterm or LBW infants, and since uncertainty exists about the balance between the putative benefits and harms, an attempt to detect, appraise and synthesise evidence from randomised controlled trials (RCTs) is merited.

OBJECTIVES

To determine the effect of feeding with formula compared with donor breast milk on growth and development in preterm or low birth weight (LBW) infants.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random participant allocation.

Types of participants

Preterm (< 37 weeks' gestation at birth) or LBW (< 2500 g) infants.

Types of interventions

Enteral feeding (orally or via gastric or transpyloric feeing tubes) with formula versus donor breast milk. The allocated milk feed may have been a supplement to maternal breast milk or have formed the entire enteral intake (sole diet).

Trials in which parenteral (intravenous) nutritional support was available during the period of advancement of enteral feeds were acceptable provided that the groups received similar treatment other than the type of milk feed.

Types of outcome measures

Primary outcomes

Growth

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

Neurodevelopment

- Death or severe neurodevelopmental disability, defined as any one, or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient < 70), auditory and visual impairment. We planned to analyse each component individually as well as part of the composite outcome.
- Neurodevelopmental scores in children aged at least 12 months, measured using validated assessment tools.

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- Cognitive and educational outcomes in children aged more than five years old.

Secondary outcomes

- All-cause mortality, during the neonatal period and prior to hospital discharge.
- Necrotising enterocolitis, confirmed at surgery or autopsy or diagnosed by at least two of the following clinical features.
  * Abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen.
  * Abdominal distension with abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both).
  * Blood in stool.
  * Lethargy, hypotonia or apnoea (or combination of these).
- Days after birth to establish full enteral feeding (independently of parenteral nutrition).
- Feeding intolerance, defined as a requirement to cease enteral feeds and commence parenteral nutrition.
- Incidence of invasive infection, as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine or from a normally sterile body space.

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal (neonatal.cochrane.org).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 5), Ovid MEDLINE (1946 to 3 May 2019), OVID Embase (1974 to 3 May 2019), OVID Maternity & Infant Care Database (1971 to 3 May 2019), and the Cumulative Index to Nursing and Allied Health Literature (1982 to 3 May 2019) using a combination of text words and MeSH terms described in Appendix 1. We limited the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply any language restrictions.

We searched ClinicalTrials.gov and the World Health Organization's International Trials Registry and Platform (www.who.int/ictrp/en/), for completed or ongoing trials.

Searching other resources

We examined reference lists in previous reviews and included studies. We searched the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to 2019), the European Society for Paediatric Research (1995 to 2019), the Royal College of Paediatrics and Child Health (2000 to 2019), and the Perinatal Society of Australia and New Zealand (2000 to 2019). 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.

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

We screened the title and abstract of all studies identified by the above search strategy and two review authors (NDE, WM) independently assessed the full articles for all potentially relevant trials. We excluded those studies that did not meet all of the inclusion criteria and we stated the reason for exclusion. We discussed any disagreements until consensus was achieved. We illustrated the screening and selection outcomes in a flowchart (PRISMA 2009).

Data extraction and management

Two review authors (NDE, WM) extracted data independently using a data collection form to aid extraction of information on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We discussed any disagreements until we reached a consensus. If data from the trial reports were insufficient, we contacted the trialists for further information.

Assessment of risk of bias in included studies

Two review authors (NDE, WM) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011).

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

We resolved any disagreements by discussion or by including a third review author (MQ). See Appendix 2 for a detailed description of risk of bias for each domain.

Measures of treatment effect

We calculated risk ratios (RRs) and risk differences (RDs) for dichotomous data and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs). When it was deemed appropriate to combine two or more study arms, we obtained the treatment effects from the combined data using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We determined the number needed to treat for an additional beneficial outcome (NNTB) or additional harmful outcome (NNTH) for a statistically significant difference in the RD.

Unit of analysis issues

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

Dealing with missing data

Where data were missing, and could not be derived as described, we approached the analysis of missing data as follows.

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- We contacted the original study investigators to request the missing data.
- Where possible, we imputed missing standard deviations (SDs) using the coefficient of variation or calculated the SD from other statistics including standard errors, CIs, t values and P values.
- If we assumed the data to be missing at random, we analysed the data without imputing any missing values.
- If we could not make this assumption, then we planned to impute the missing outcomes with replacement values, assuming all to have a poor outcome. We planned sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

Two review authors (NDE, WM) assessed clinical heterogeneity, with a meta-analysis conducted only when both agreed that study participants, interventions and outcomes were sufficiently similar.

We examined the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and described the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high heterogeneity ($I^2 > 50\%$), we would explore the possible causes (for example, differences in study design, participants, interventions or completeness of outcome assessments).

Assessment of reporting biases

If more than 10 trials were included in a meta-analysis, we planned to examine a funnel plot for asymmetry.

Data synthesis

We used fixed-effect models for meta-analysis (as per Cochrane Neonatal recommendations). Where moderate or high heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Certainty of evidence

We assessed the certainty of evidence for the main comparisons at the outcomes level using the GRADE approach to assess the certainty of evidence for the following outcomes: growth, neurodevelopmental disability, all-cause mortality, and necrotising enterocolitis (Schünemann 2013; see Appendix 3).

Two review authors (NDE, WM) independently assessed the certainty of the evidence for each of these outcomes. We considered evidence from RCTs as high certainty but downgraded one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the Guideline Development Tool to create a 'Summary of findings' table to report the certainty of the evidence (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses of trials to compare:

- formula versus donor breast milk given as (i) a sole diet or (ii) a supplement to maternal expressed breast milk;
- formula versus donor breast milk that is (i) unfortified or (ii) nutrient-fortified (defined as supplementation with more than one of the following components: protein, fat, carbohydrate or minerals).

RESULTS

Description of studies

Results of the search

See: Figure 1.

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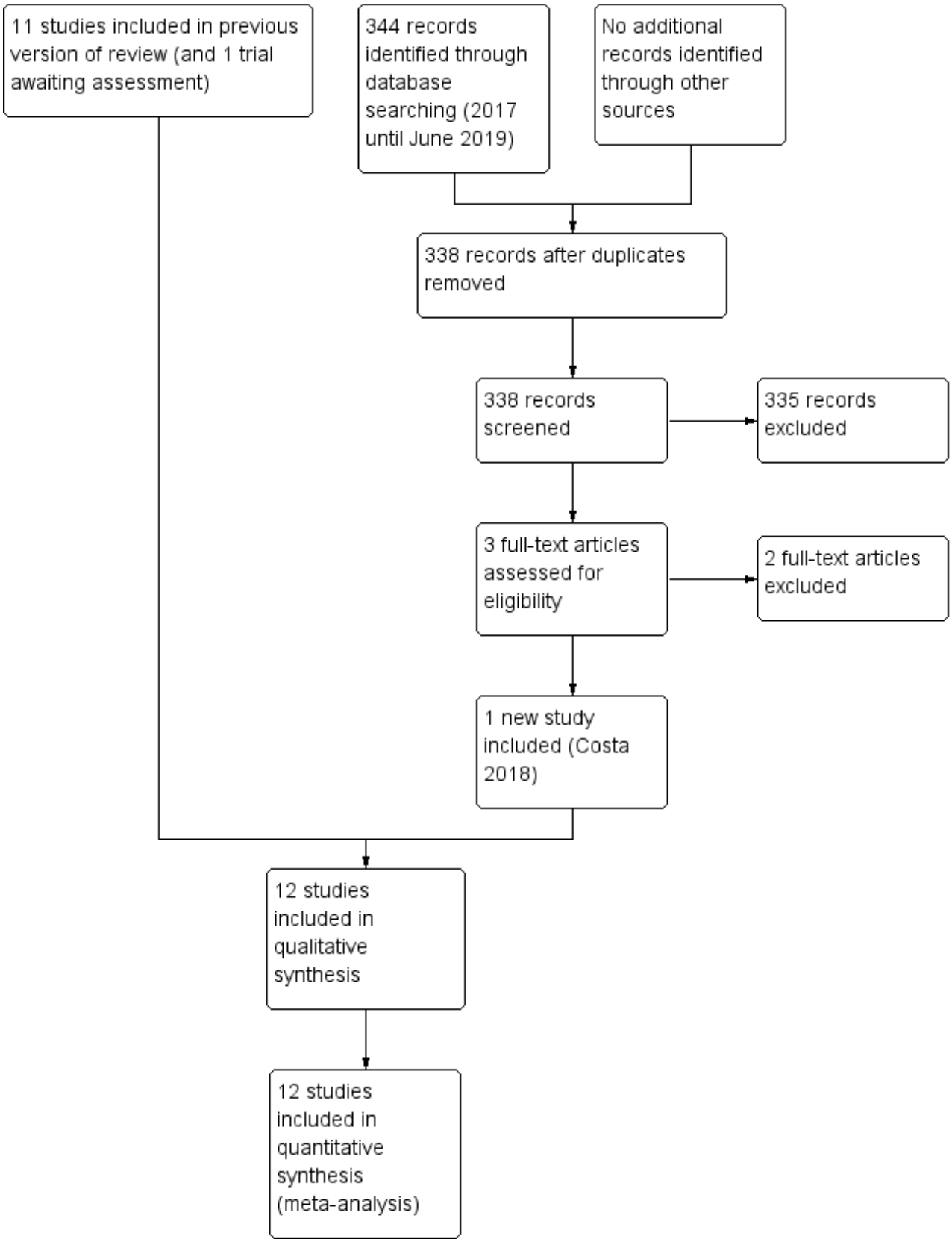
Figure 1. Study flow diagram: 2019 review update.



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We included one new trial (12 trials in total) (Costa 2018). We excluded two new full-text reports (Brandstetter 2018; Castellano 2019) (14 reports in total).

One report is awaiting assessment (Perez 2015).

We identified four ongoing trials (See: Characteristics of ongoing studies).

Included studies

Twelve trials fulfilled the review eligibility criteria (Raiha 1976; Davies 1977; Schultz 1980; Gross 1983; Tyson 1983; Lucas 1984a; Lucas 1984b; Schanler 2005; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016; Costa 2018).

All trials were undertaken in neonatal units in Europe and North America. Seven of the trials were conducted more than 30 years ago (Raiha 1976; Davies 1977; Schultz 1980; Gross 1983; Tyson 1983; Lucas 1984a; Lucas 1984b). Five trials have been undertaken since the year 2000 (Schanler 2005; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016; Costa 2018). For further details see Characteristics of included studies.

Participants

A total of 1879 infants took part in the included trials. Most participants were clinically stable infants of gestational age at birth < 32 weeks' or birth weight < 1800 g. Most trials excluded infants who were small for gestational age at birth and infants with congenital anomalies or gastrointestinal or neurological problems.

Interventions

The trials varied according to type of formula (term or preterm), and whether the intervention was a sole diet or a supplement to mother's own milk.

- Four trials compared feeding with term formula versus unfortified donor breast milk (Raiha 1976; Davies 1977; Schultz 1980; Gross 1983). In all of these trials, term formula or donor breast milk was the sole diet.
- Eight trials compared feeding with preterm formula versus donor breast milk, either as the sole diet (Tyson 1983; Lucas 1984a; Cristofalo 2013), or as a supplement to maternal breast milk (Lucas 1984b; Schanler 2005; Corpeleijn 2016; O'Connor 2016; Costa 2018).

The trials varied according to type of donor breast milk, and whether donor breast milk feeds were nutrient-fortified or not.

- Five trials used donor breast milk collected from mothers who had delivered an infant at term (Raiha 1976; Davies 1977; Schultz 1980; Lucas 1984a; Lucas 1984b). Two of these trials used 'drip' breast milk (Lucas 1984a; Lucas 1984b). One trial used preterm donor breast milk (Schanler 2005), one trial used both term and preterm donor milk (Gross 1983), and five trials did not specify the type of donor breast milk (Tyson 1983; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016; Costa 2018).
- In all trials except Tyson 1983, the donor breast milk was pasteurised.
- Four trials used donor breast milk with multinutrient fortifier added empirically or as indicated (Schanler 2005; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016). Cristofalo 2013 used human milk-based fortifier, and the other trials used cow's milk-based fortifier.

In general, feeds were allocated for several weeks, or until participating infants reached a specified body weight (generally > 2 kg). One trial used the allocated feed for only the first 10 days after birth (or earlier if the infant was transferred from the recruiting centre). Infants then received preterm formula if own mother's milk was insufficient (Corpeleijn 2016).

Outcomes

The most commonly reported outcomes were growth parameters during the study period or until hospital discharge. Most reports gave information on adverse outcomes, including feeding intolerance and the incidence of necrotising enterocolitis. Four trials reported growth or neurodevelopmental outcomes assessed during and after infancy following hospital discharge (Gross 1983; Lucas 1984a; Lucas 1984b; O'Connor 2016).

Excluded studies

We excluded 14 studies following full-text review (Narayanan 1982; Svenningsen 1982; Jarvenpaa 1983; Cooper 1984; Putet 1984; O'Connor 2003; Sullivan 2010; Hair 2014; Colaizy 2015; Marseglia 2015; Perrella 2015; Tewari 2018; Brandstetter 2018; Castellano 2019). The reasons for exclusion are described in the table Characteristics of excluded studies.

Studies awaiting classification

One report is awaiting translation and assessment (Perez 2015).

Ongoing studies

We identified four ongoing trials (see: Characteristics of ongoing studies).

Risk of bias in included studies

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

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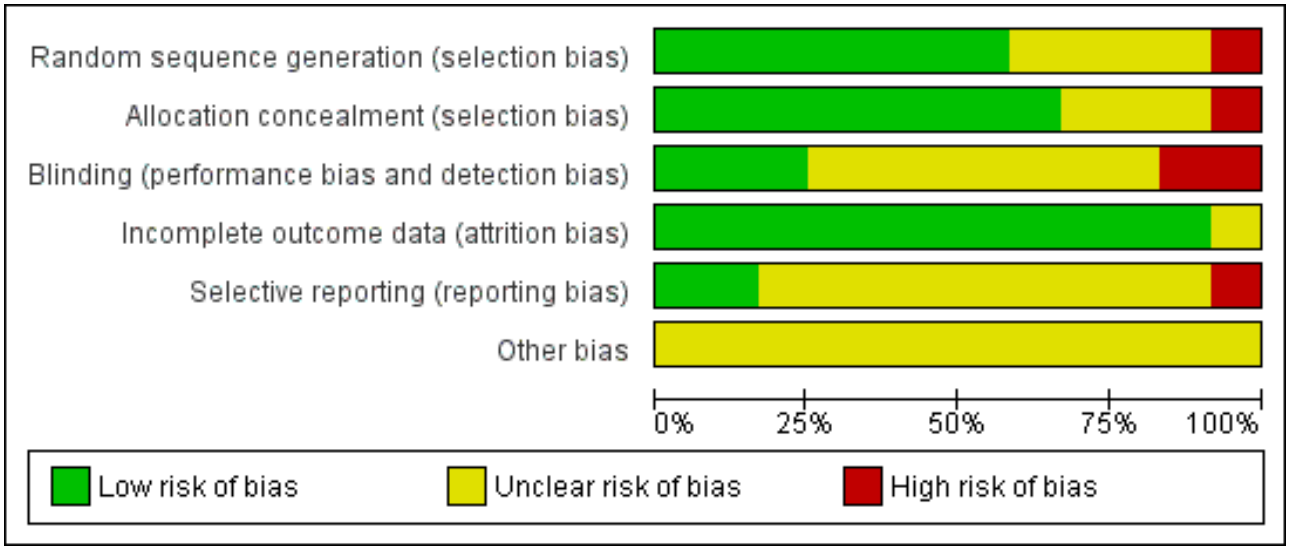
Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Six trials reported adequate allocation concealment methods (sealed, numbered envelopes; central randomisation in blocks) and we assessed these trials as being at low risk of bias (Lucas 1984a; Lucas 1984b; Tyson 1983; Corpeleijn 2016; O'Connor 2016; Costa 2018). The other trials did not report methods of allocation concealment. One quasi-RCT randomly allocated participants to one of the four formula arms, and allocated every fifth infant to the donor breast milk arm (Raiha 1976); we assessed this trial as being at high risk of selection bias.

Blinding

Four trials blinded the staff or caregivers to the treatments and we assessed them as being at low risk of bias (Schanler 2005; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016). Three trials did not mask the staff and we assessed them as being at high risk of bias (Tyson 1983; Lucas 1984a; Lucas 1984b). The other trial reports did not state whether staff were masked.

Most of the trials did not specify whether the outcome assessors were masked to the feeding arms (unclear risk of bias). In four trials staff were masked to the post-hospital discharge outcomes and we assessed them as being at low risk of bias (Lucas 1984a; Lucas 1984b; Corpeleijn 2016; O'Connor 2016).

Incomplete outcome data

Most trials reported complete follow-up for the in-hospital outcomes assessment and we assessed them as being at low risk of attrition bias. In three trials, infants who developed complications (5% to 10% of the total enrolled) were withdrawn from the study and therefore the in-hospital growth data for these infants were not presented (Raiha 1976; Gross 1983; Tyson 1983). In the trials that reported data for long-term outcomes, more than 80% of participants were assessed (low risk of bias) (Gross 1983; Lucas 1984a; Lucas 1984b; O'Connor 2016).

Selective reporting

We assessed Corpeleijn 2016 as being at high risk of reporting bias. Corpeleijn 2016 did not report protocol-specified outcome data for short-term growth rate, bone density, Bayley Scores of Infant Development III (at 2 years of age), and growth rate at two years of age. Most of the other trials were at unclear risk of bias as protocols were not available for assessment.

Effects of interventions

See: **Summary of findings for the main comparison** Formula versus donor breast milk for feeding preterm or low birth weight infants

Primary outcomes

Growth

Time to regain birth weight

Meta-analysis of data from Raiha 1976, Gross 1983 and Costa 2018 showed that the formula-fed group regained birth weight more quickly (mean difference (MD) -3.08 days, 95% confidence interval (CI) -4.38 to -1.77; I^2 = 37%; 3 trials, 236 participants; Analysis 1.1).

Schultz 1980 did not detect a statistically significant difference, but standard deviations (SDs) were not reported and we could not include the data in the meta-analysis.

Lucas 1984a reported the median time to regain birth weight as lower in the formula-fed infants (10 versus 16 days). Lucas 1984b did not find a statistically significant difference (13 versus 15 days). SDs were not reported and we could not include the data in the meta-analysis.

The other trials did not report time to regain birth weight.

Rate of weight gain

Formula-fed infants had a higher rate of weight gain but with high heterogeneity in the estimate of this effect (MD 2.51, 95% CI 1.93 to 3.08 g/kg/day; I^2 = 90%; 9 trials, 1028 participants; moderate-

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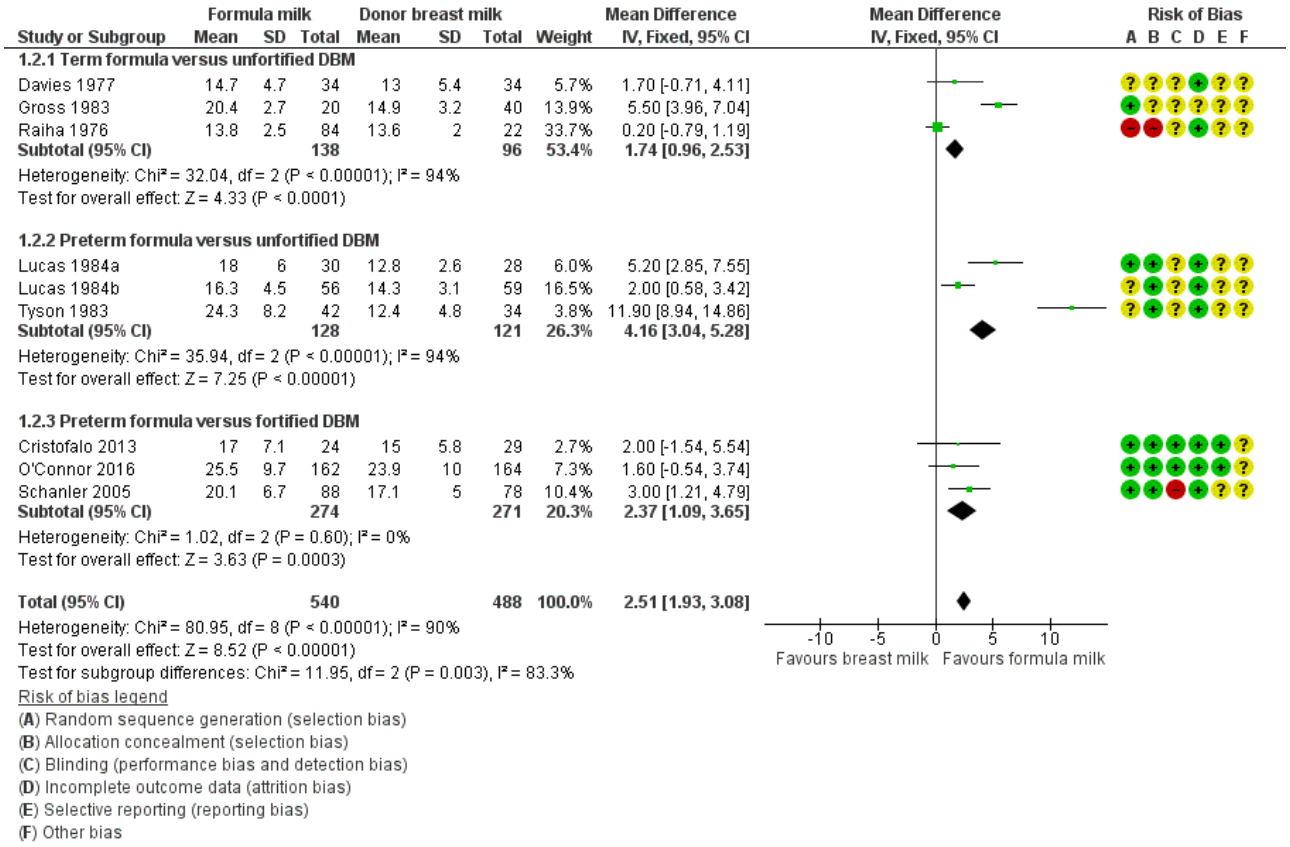
certainty evidence; Summary of findings for the main comparison; Analysis 1.2). Significant subgroup differences existed with the largest effect size for the comparison of preterm formula with unfortified donor breast milk (MD 4.16, 95% CI 3.04 to 5.28 g/kg/day) (Figure 3).

Figure 3. Forest plot of comparison: 1 Formula (term or preterm) versus donor breast milk, outcome: 1.2 Weight gain (g/kg/day).



Schultz 1980 and Corpeleijn 2016 did not report rate of weight gain.

Costa 2018 did not detect a between-group difference in average weight at 15 days after birth or at 36 weeks' post-menstrual age.

Linear growth

Formula-fed infants had a higher rate of increase in crown-heel length but with high heterogeneity in the estimate of this effect (MD 1.21, 95% CI 0.77 to 1.65 mm/week; I^2 = 68%; 8 trials, 820 participants; moderate-certainty evidence; Summary of findings for the main comparison; Analysis 1.3; Analysis 1.4; Analysis 1.5). Significant subgroup differences existed with the largest effect size for the comparison of preterm formula with unfortified donor breast milk (MD 2.01, 95% CI 1.21 to 2.81 mm/week) (Figure 4).

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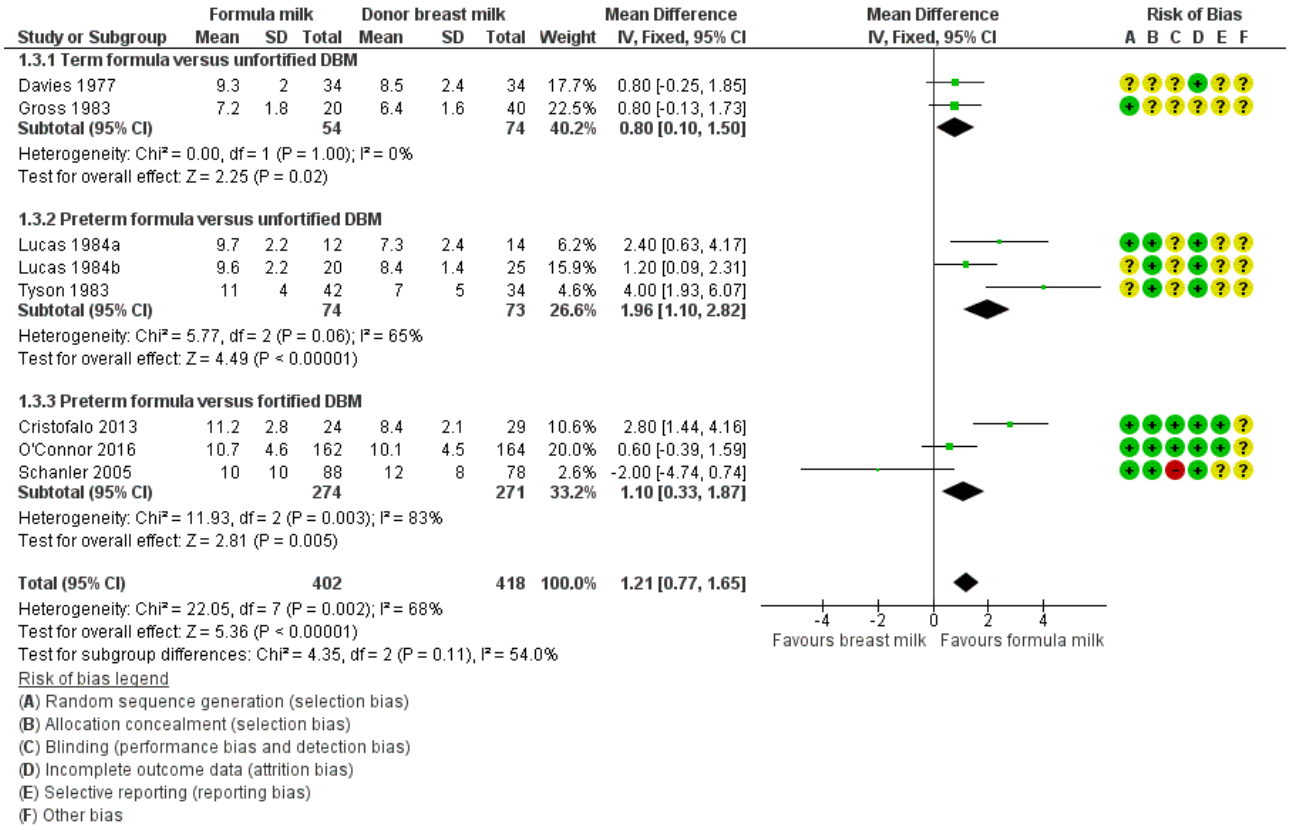
Figure 4. Forest plot of comparison: 1 Formula (term or preterm) versus DBM (unfortified of fortified), outcome: 1.3 Linear growth (crown-heel length mm/week).



Raiha 1976 reported higher rates of increase in crown-rump (MD 0.59, 95% CI 0.08 to 1.10 mm/week) and femoral length (MD 0.34, 95% CI 0.13 to 0.55 mm/week) in the formula-fed group.

Schultz 1980 and Corpeleijn 2016 did not report rate of linear growth.

Costa 2018 did not detect a between-group difference in average length at 15 days after birth or at 36 weeks' post-menstrual age.

Head growth

Formula-fed infants had a higher rate of increase in occipitofrontal head circumference but with high heterogeneity in the estimate of this effect (MD 0.85, 95% CI 0.47 to 1.23 mm/week; I^2 = 74%; 8 trials, 894 participants; moderate-certainty evidence; Summary of findings for the main comparison; Analysis 1.6). Significant subgroup differences existed with the largest effect size for the comparison of preterm formula with unfortified donor breast milk (MD 4.16, 95% CI 3.04 to 5.28 g/kg/day) (Figure 5).

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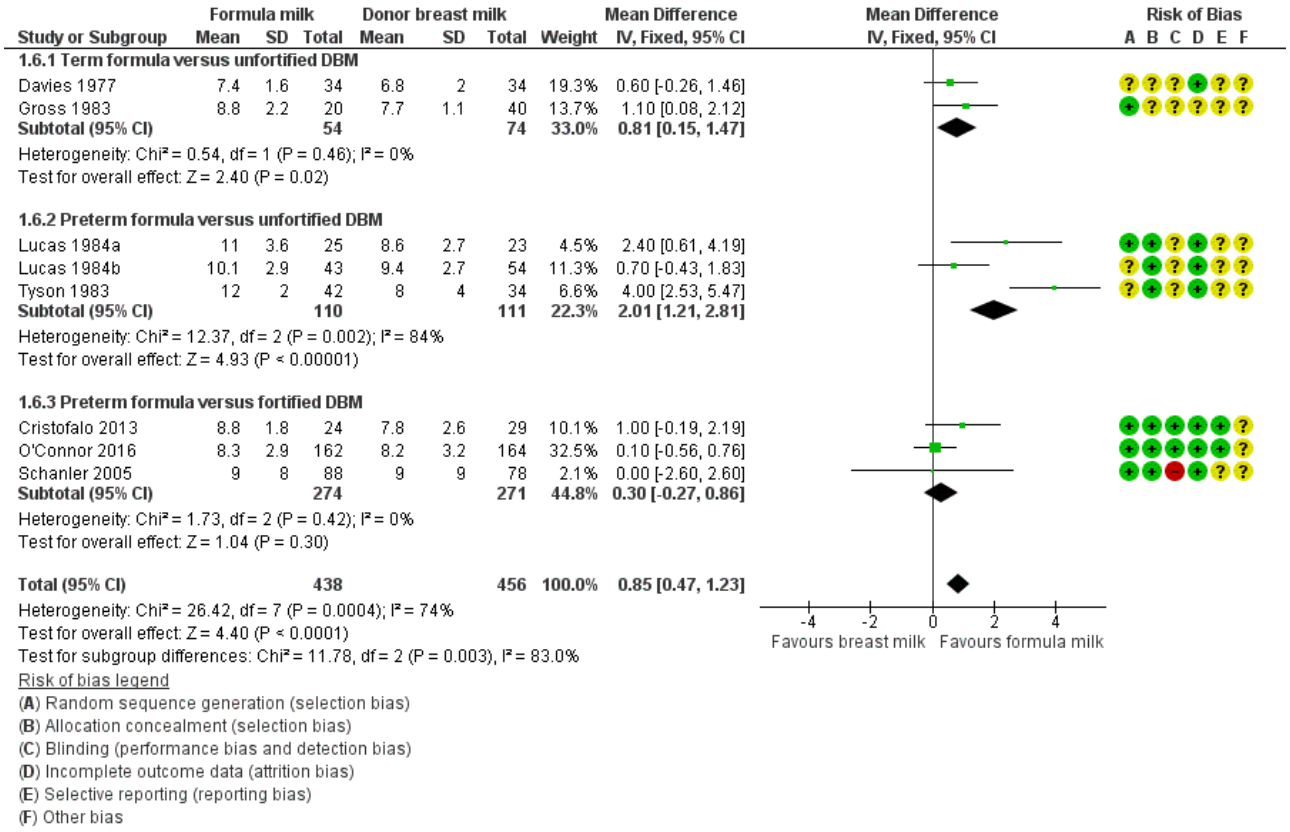
Figure 5. Forest plot of comparison: 1 Formula (term or preterm) versus DBM (unfortified of fortified), outcome: 1.6 Head growth (mm/week).



Raiha 1976, Schultz 1980 and Corpeleijn 2016 did not report rate of head growth.

Costa 2018 did not detect a between-group difference in average head circumference at 15 days after birth or at 36 weeks' post-menstrual age.

Long-term growth

Post-hospital discharge growth was reported by Lucas 1984a and Lucas 1984b. Neither individual study, nor meta-analyses of data from both studies, showed differences in the weight, length or head circumference at nine months, 18 months or 7.5 to eight years post-term; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15.

Neurodevelopment

Death or severe neurodevelopmental disability

These composite data are not yet available from the trials that assessed neurodevelopmental outcomes.

Neurodevelopmental scores

Four trials have reported neurodevelopmental outcomes or assessment scores in children aged at least 12 months, measured using validated assessment tools (Gross 1983; Lucas 1984a; Lucas 1984b; O'Connor 2016):

Gross 1983 stated that there was "no difference" in Bayley Mental or Psychomotor Developmental Indices at 15 months post-term (numerical data not available).

Lucas 1984a and Lucas 1984b, or a meta-analysis of data from both, did not show differences in Bayley Psychomotor and Mental Development Indices at 18 months' corrected age.

- Mental Development Index: MD 1.24, 95% CI -2.62 to 5.09 (Analysis 1.16).
- Psychomotor Development Index: MD -0.32, 95% CI -3.48 to 2.79 (Analysis 1.17).

"Severe neurodevelopmental disability" (Amiel-Tison 1986 classification) was assessed in children aged 18 months post-term in two trials. Neither Lucas 1984a nor Lucas 1984b, or a meta-analysis of data from both trials, showed a difference: typical RR 1.21 (95% CI 0.62 to 2.35; I^2 = 17%; 2 trials, 400 participants); RD -0.02 (95% CI -0.04 to 0.17); moderate-certainty evidence; Summary of findings for the main comparison; Analysis 1.18).

O'Connor 2016 did not show any differences in the mean scores on Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) assessments at 18 to 22 months' corrected age.

- Cognitive: MD 1.60, 95% CI -2.71 to 5.91 (Analysis 1.19).
- Language: MD 3.00, 95% CI -2.01 to 8.01 (Analysis 1.19).
- Motor: MD 2.20, 95% CI -2.07 to 6.47 (Analysis 1.19).

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There were not any differences in the proportion of children with Bayley-III scores < 70 in O'Connor 2016.

- Cognitive: RR 0.82, 95% CI 0.40 to 1.68 (Analysis 1.20); RD -0.02, 95% CI -0.08 to 0.05.
- Language: RR 0.78, 95% CI 0.47 to 1.30 (Analysis 1.20); RD -0.04 (95% CI -0.13 to 0.04).
- Motor: RR 0.73, 95% CI 0.37 to 1.44 (Analysis 1.20); RD -0.03 (95% CI -0.10 to 0.04).

There were not any differences in the proportion of children diagnosed with cerebral palsy, or hearing or visual impairment in O'Connor 2016.

- Cerebral palsy: RR 0.51, 95% CI 0.21 to 1.23 (Analysis 1.21); RD -0.05 (95% CI -0.10 to 0.01).
- Hearing impairment: RR 1.02, 95% CI 0.30 to 3.45 (Analysis 1.22); RD 0.00 (95% CI -0.04 to 0.04).
- Visual impairment: RR (not estimable - no events; Analysis 1.23); RD 0.00 (95% CI -0.01 to 0.01).

Cognitive and educational outcomes in children aged more than five years old

Lucas 1984a and Lucas 1984b assessed cognitive outcomes (verbal and performance intelligence quotient) in about 20% of participants at ages eight and 16 years. Numerical data were not reported for the individual trials but rather were combined with data from another trial undertaken by the same investigators that compared feeding preterm infants with nutrient-enriched versus standard formula (Isaacs 2009).

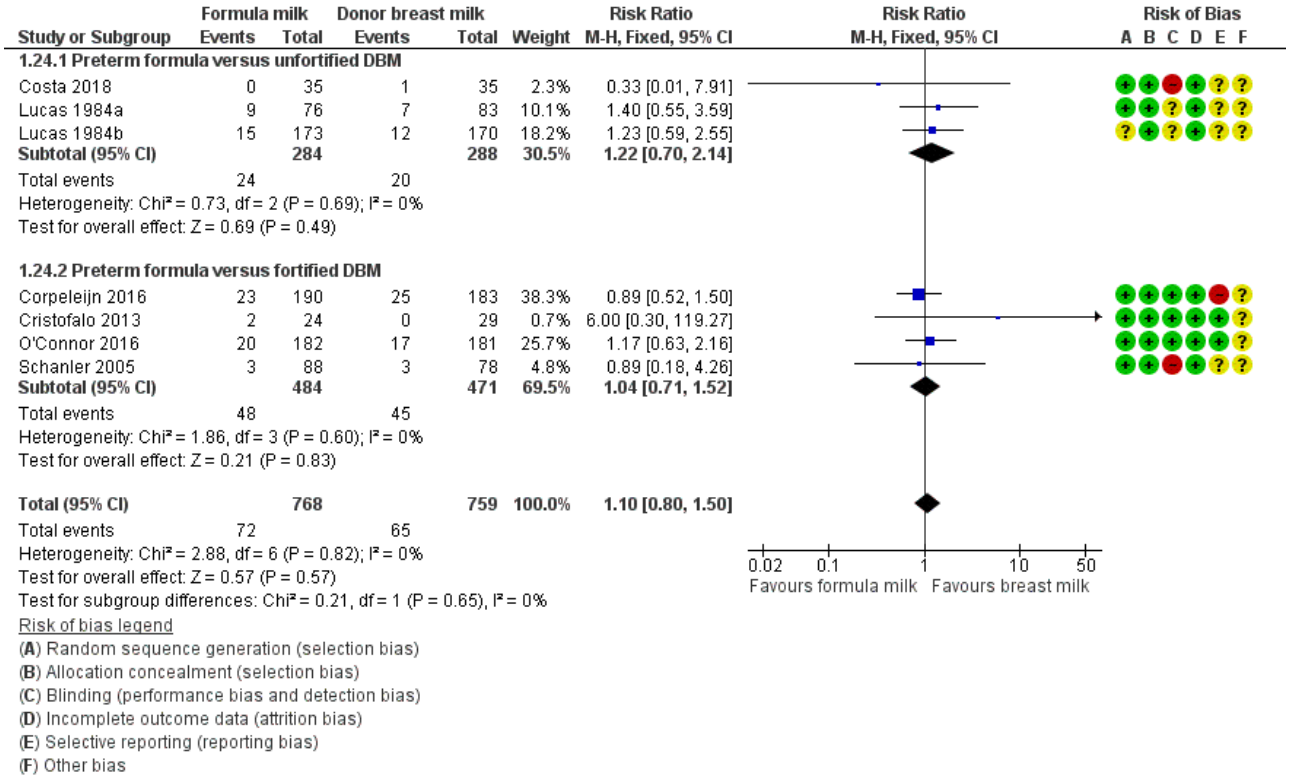
O'Connor 2016 has not yet reported any cognitive and educational outcomes in children aged more than five years old.

Secondary outcomes

All-cause mortality

Data were available from seven trials. Two trials reported mortality until nine months post-term (Lucas 1984a; Lucas 1984b). The other trials reported mortality until hospital discharge (Schanler 2005; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016; Costa 2018). None showed a difference between the groups. Since it is likely that most infant mortality in this population occurred before hospital discharge, we combined the data from the trials in a meta-analysis: RR 1.10, 95% CI 0.80 to 1.50; I^2 = 0%; 7 trials, 1527 participants; moderate-certainty evidence; Summary of findings for the main comparison; Analysis 1.24). There were not any significant subgroup differences (Figure 6).

Figure 6. Forest plot of comparison: 1 Formula (term or preterm) versus DBM (unfortified of fortified), outcome: 1.24 All-cause mortality.



Necrotising enterocolitis

Meta-analysis of data available from nine trials showed a higher risk of necrotising enterocolitis in the formula-fed group: RR 1.87, 95% CI 1.23 to 2.85; I^2 = 14%; 9 trials, 1675 participants; RD 0.03, 95% CI 0.01 to 0.05; number needed to treat for an additional harmful outcome (NNTH) 33 (95% CI 20 to 100); moderate-certainty evidence; Summary of findings for the main comparison; Analysis

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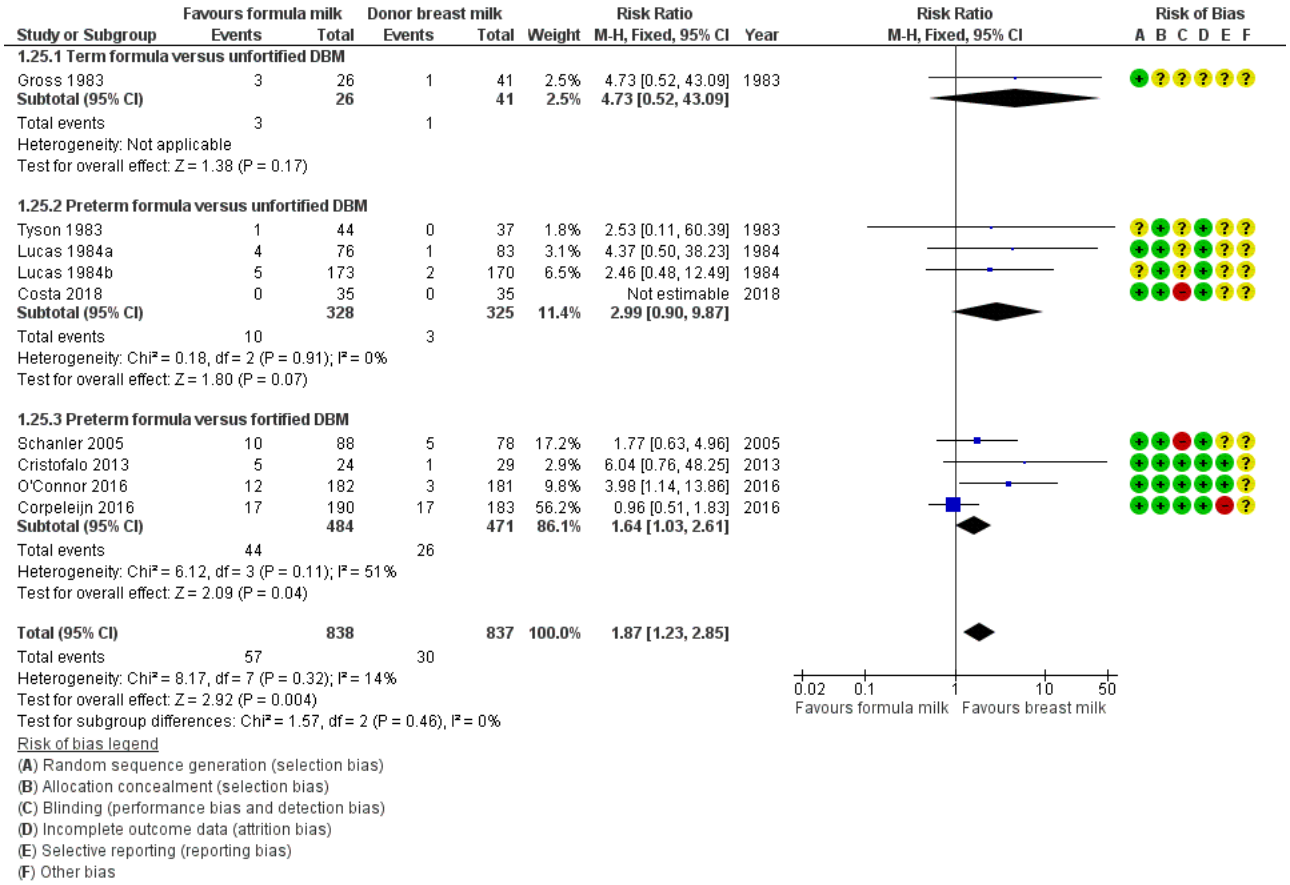
1.25). There were not any significant subgroup differences (Figure 7).

Figure 7. Forest plot of comparison: 1 Formula (term or preterm) versus DBM (unfortified of fortified), outcome: 1.25 Necrotising enterocolitis.



Days after birth to establish full enteral feeding

This was reported by three trials. A meta-analysis of data from Cristofalo 2013 and Costa 2018 did not show a difference (MD 0.33, 95% CI -2.57 to 3.23 days; Analysis 1.26). There were not any significant subgroup differences.

Corpeleijn 2016 reported no difference in median time to full feeds independent of parenteral nutrition (12 versus 11 days) but did not provide sufficient data for inclusion in a meta-analysis.

Feeding intolerance

Meta-analysis of data from Gross 1983 and Tyson 1983 showed a higher incidence of feeding intolerance in the formula-fed group (RR 4.92, 95% CI 1.17 to 20.70; RD 0.10, 95% CI 0.01 to 0.19; NNTH 10, 95% CI 5 to 100; Analysis 1.27).

Lucas 1984a reported that significantly more infants in the formula-fed group failed to tolerate full enteral feeds by two weeks after birth (25/76 versus 9/83 in the donor breast milk group) and by three weeks after birth (13/76 versus 4/83).

Incidence of invasive infection

Meta-analysis of data available from five trials did not show a difference in invasive infection (RR 0.94, 95% CI 0.79 to 1.12; I^2 = 37%; 5 trials, 1025 infants; Analysis 1.28). There were not any significant subgroup differences.

Subgroup analysis: formula versus donor breast milk as (i) sole diet or (ii) supplement to maternal expressed breast milk

- Seven trials compared feeding with formula versus donor breast milk as a sole diet (Raiha 1976; Davies 1977; Schultz 1980; Gross 1983; Tyson 1983; Lucas 1984a; Cristofalo 2013).
- Five trials compared feeding with formula versus donor breast milk as a supplement to maternal expressed breast milk (Lucas 1984b; Schanler 2005; Corpeleijn 2016; O'Connor 2016; Costa 2018).

Growth

Meta-analyses did not show subgroup differences for rate of weight gain (Analysis 2.1), or increase in crown-heel length (Analysis 2.2).

Subgroup comparisons showed significant differences for head growth.

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- Sole diet: MD 1.36, 95% CI 0.85 to 1.88 mm/week.
- Supplement: MD 0.24, 95% CI -0.32 to 0.80 mm/week.
- Test for subgroup differences: $Chi^2 = 8.37$, df = 1 (P = 0.004), $I^2 = 88.1\%$ (Analysis 2.3).

Meta-analyses of data from Lucas 1984a (sole diet) and Lucas 1984b (supplemental) did not show any subgroup differences for long-term growth (Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12).

Neurodevelopment

Meta-analyses of data from Lucas 1984a (sole diet) and Lucas 1984b (supplemental) did not show any subgroup differences for neurodevelopmental outcomes (Analysis 2.13; Analysis 2.14; Analysis 2.15).

Secondary outcomes

Meta-analyses did not show significant subgroup differences for all-cause mortality (Analysis 2.16), or necrotising enterocolitis (Analysis 2.17).

Subgroup comparisons showed significant differences for incidence of invasive infection.

- Sole diet: RR 1.43, 95% CI 0.97 to 2.11; RD 0.24, 95% CI -0.00 to 0.48.
- Supplement: RR 0.89, 95% CI 0.73 to 1.08; RD -0.03, 95% CI -0.09 to 0.02.
- Test for subgroup differences: $Chi^2 = 4.70$, df = 1 (P = 0.03), $I^2 = 78.7\%$ (Analysis 2.18).

DISCUSSION

Summary of main results

We included 12 randomised controlled trials (RCTs) in which a total of 1879 preterm or low birth weight (LBW) infants participated. Meta-analyses show that infants who receive formula regain birth weight earlier and have higher in-hospital rates of weight gain, linear growth, and head growth than infants who receive donor breast milk. These effects on growth parameters are greater in trials that compare feeding with nutrient-enriched preterm formula rather than standard term formula versus donor breast milk. Follow-up of the infants who participated in two of the largest trials did not show any effects on long-term growth. None of the trials that assessed neurodevelopment beyond infancy showed any significant effects.

Meta-analysis of data from eight trials shows that feeding with formula rather than donor breast milk increases the risk of necrotising enterocolitis in preterm and LBW infants.

Overall completeness and applicability of evidence

These findings should be interpreted with caution. Substantial heterogeneity in the meta-analyses of weight gain, linear growth, and head growth limits the validity of the pooled estimates of effect size. Many of the trials that contributed data to these meta-analyses were undertaken more than 20 years ago and the trials used different inclusion criteria and varied with respect to the type of formula and donor breast milk. Five trials have been undertaken in the past 20 years and four of these trials compared feeding with preterm formula versus donor breast milk with added multinutrient fortifier (Schanler 2005; Cristofalo 2013; Corpeleijn 2016; O'Connor 2016). Subgroup analyses of data from these trials, which are more likely to be applicable to current practice in high-income countries, where nutrient fortification of breast milk is commonly undertaken, shows higher rates of weight gain and linear growth in formula-fed infants, but no effect on head growth.

The pooled estimate from meta-analysis of data from nine trials suggests that one extra case of necrotising enterocolitis will occur in every 33 infants who receive formula. This beneficial effect of donor breast milk exists even when donor breast milk is given as a supplement to maternal breast milk, rather than as a sole diet, and when the donor breast milk is nutrient-fortified. The subgroup meta-analysis of four trials that compared feeding infants with preterm (nutrient-enriched) formula versus nutrient-fortified donor breast milk was moderately heterogeneous ($I^2 = 51\%$). A possible explanation is that the trials differed in the intensity and duration of exposure to the intervention. Infants participating in Corpeleijn 2016 (the trial that contributed most to the heterogeneity) received the trial interventions for only the first 10 days after birth as maternal (mother's own) breast milk was widely available by this stage. In the other three trials, in contrast, infants received the allocated intervention for up to 90 days or the duration of birth hospitalisation (Schanler 2005; Cristofalo 2013; O'Connor 2016). It is plausible that donor breast milk is less effective in preventing necrotising enterocolitis in settings where formula (rather than maternal breast milk) use is more prevalent.

Most of the trials included in the meta-analysis did not mask caregivers and assessors to the intervention. This methodological weakness may have resulted in surveillance and ascertainment biases that contributed to the higher rate of detection of necrotising enterocolitis in formula-fed infants. Caution should be exercised in applying these data to growth-restricted preterm infants or sick infants since these infants, although at high risk of developing necrotising enterocolitis, were ineligible to participate in many of the included trials.

The data in this review are from trials undertaken in high-income countries. In low- or middle-incomes countries, the immunoactive properties of breast milk may confer advantages that outweigh the lower rate of short-term growth. In India, a RCT in LBW infants "at risk of infection" found that serious infections (diarrhoea, pneumonia, septicaemia) were less common in infants allocated to received "expressed human milk" versus formula milk (Narayanan 1982). "Expressed human milk" in this study referred to a mixture of maternal and donor breast milk. As we could not separate these into subgroups, we did not include the data in the review.

Quality of the evidence

The GRADE certainty of evidence was moderate for rates of weight gain, linear growth, and head growth (downgraded for high levels of heterogeneity) and was moderate for neurodevelopmental disability, all-cause mortality, and necrotising enterocolitis (downgraded for imprecision) (Summary of findings for the main comparison).

Some of the trials contained various weaknesses in methodological quality, specifically concern about allocation concealment methods in four trials, and about methods to ensure masking in most of the trials. Parents, caregivers, clinicians and investigators

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were likely to have been aware of the treatment group to which infants had been allocated and this knowledge may have affected some care practices or investigation strategies, including thresholds for screening or diagnosing for necrotising enterocolitis.

Most of the included trials were funded or supported by the manufacturers of the formulas being assessed, but the funders were not involved in trial design or analysis. There remains some concern that formula manufacturers may promote study findings of trials of specialist formulas selectively as part of a marketing strategy that subverts UNICEF Baby Friendly Initiative regulations (Cleminson 2015).

Potential biases in the review process

The main concern with the review process is the possibility that the findings are subject to publication and other reporting biases, including more availability of numerical data for inclusion in meta-analyses from trials that reported statistically significant or clinically important effects. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and searching the proceedings of the major international perinatal conferences to identify trial reports that are not (or not yet) published in full form in academic journals. However, we cannot be sure whether other trials have been undertaken, but not reported, and the concern remains that such trials are less likely than published trials to have detected statistically significant or clinically important effects. The meta-analyses that we performed did not contain sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-certainty evidence that feeding with formula, particularly preterm formula, compared with donor breast milk increases rates of weight gain, linear growth, and head growth in preterm or low birth weight (LBW) infants in hospital. Formula feeding is associated with a near-doubling of the risk of necrotising enterocolitis. These is no evidence of an effect on all-cause mortality, or on long-term growth and neurodevelopment. There are limited data from RCTs on the comparison of feeding with formula milk versus nutrient-fortified human milk. This limits the implications for practice from this review as nutrient fortification of human milk is now a common practice in neonatal care (Williams 2016).

Implications for research

Further RCTs of feeding with formula versus donor breast milk in situations where the expressed breast milk of the preterm or LBW infant's mother is not consistently available are needed. Several such trials are in progress and these propose to recruit more than 1100 infants in total (Characteristics of ongoing studies). Incorporating the data from these trials in meta-analyses should generate more precise estimates of effect sizes, and strengthen the applicability of the trial evidence base to current practice. In addition to clinical effectiveness, future research efforts to inform practice and policy should assess acceptability and cost-effectiveness (Buckle 2017).

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

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

Corpeleijn 2016

Methods	Randomised controlled trial
Participants	373 VLBW infants with insufficient maternal breast milk during the first 10 days after birth. Six neonatal units in the Netherlands, 2012 to 2014
Interventions	Preterm formula (N = 190) versus donor breast milk (N = 183) given as a supplement to maternal breast milk (with cow's milk-based multinutrient fortifier)
Outcomes	Invasive infection, NEC, or mortality during the first 60 days after birth (composite)
Notes	Intervention given during first 10 days after birth only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Online randomisation software"
Allocation concealment (selection bias)	Low risk	Computer randomised
Blinding (performance bias and detection bias) All outcomes	Low risk	Families and clinicians "blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	99% assessment for primary outcome
Selective reporting (reporting bias)	High risk	Protocol specified short-term growth rate, bone density. Bayley Scores of Infant Development III (at 2 years of age), growth rate (at 2 years of age) as outcomes to be assessed - these are not reported
Other bias	Unclear risk	Funded by Mead Johnson Nutrition

Costa 2018

Methods	Randomised controlled trial
Participants	70 infants (< 33 weeks') with insufficient maternal breast milk during the first 14 days after birth. One neonatal unit in Italy, 2015
Interventions	Preterm formula (N = 35) versus donor breast milk (N = 35) given as a supplement to maternal breast milk
Outcomes	Time to full enteral feeding (150 mL/kg/day), invasive infection, NEC, bronchopulmonary dysplasia (BPD), or mortality until 36 weeks' post-menstrual age

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Costa 2018 *(Continued)*

Notes	Fortification policy not described (author contacted June 2019 for clarification: simonetta.costa@policlinicogemelli.it)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated list of random numbers"
Allocation concealment (selection bias)	Low risk	"...sequence was concealed from researchers"
Blinding (performance bias and detection bias) All outcomes	High risk	Families and clinicians not masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete assessment for primary outcome
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder not stated

Cristofalo 2013

Methods	Randomised controlled trial
Participants	53 newborn infants: birth weight 500 g to 1250 g Exclusions: major congenital abnormalities, high likelihood of transfer to a non-study site after 48 hours Seven neonatal intensive care units: six in USA, one in Austria (Probably) 2010 to 2012
Interventions	Preterm formula milk (N = 24) versus fortified (with human milk-based fortifier), pasteurised donor breast milk (N = 29). Assigned until 91 days after birth, or discharge, or oral feeding at least 50% of feeds
Outcomes	Duration of parenteral nutrition, growth, respiratory support, and NEC
Notes	Additional information on methods courtesy of Dr Cristafalo (April 2014)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated centrally in permuted blocks stratified by investigational site
Allocation concealment (selection bias)	Low risk	Allocation outcome provided to an individual at each site who was not connected with the evaluation of outcomes for participants
Blinding (performance bias and detection bias)	Low risk	Investigators, caregivers, and families were masked

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Cristofalo 2013 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up
Selective reporting (reporting bias)	Low risk	No deviations from protocol
Other bias	Unclear risk	Funded by Prolacta Bioscience

Davies 1977

Methods	Randomised controlled trial
Participants	68 preterm infants: 28 to 36 weeks in 2 strata Exclusions: multiple births, congenital abnormalities and chromosomal disorders, congenital infection. Growth-restricted infants (< 5th percentile) may also have been excluded Department of Child Health, University Hospital of Wales, Cardiff 1972 to 1973
Interventions	Term formula milk (N = 34) versus unfortified, pasteurised donor breast milk (N = 34). Assigned from birth for 2 months
Outcomes	Rates of weight gain, increase in head circumference and length from birth until 1 month and from 1 month until 2 months
Notes	Infants of mothers who wished to breastfeed were initially given expressed breast milk if unable to feed naturally. There were only 2 such infants; their feeding group was not specified and the results for these infants are not presented separately in the paper. Given that this applies to only 2 out of 68 infants, we have included this study in the review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder not stated (likely to be unfunded)

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Gross 1983

Methods	Randomised controlled trial
Participants	67 preterm infants (27 to 33 weeks) Birth weight < 1600 g. Excluded if "congenital anomaly or major disease" Department of Pediatrics, Duke University, USA 1980 to 1982
Interventions	Term formula milk (N = 26) versus unfortified, pasteurised donor breast milk (N = 41). Feeds were assigned until the infant reached a weight of 1800 g or until withdrawn from the study because of feeding intolerance or NEC
Outcomes	Time to regain birth weight Mean daily gain in weight, length and head circumference, from regaining birth weight until reaching 1800 g Data on adverse events can be determined, although these were not primary endpoints of the study
Notes	Although the report gave information on adverse outcomes, the 7 affected infants were withdrawn from the study and not included in the analyses of growth rates. Therefore, growth data are reported for 20 infants in each arm of the trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Method not stated "Any infant withdrawn from the study was replaced by the next one enrolled"; implies lack of allocation concealment for these infants
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 out of 67 (10%) with adverse outcomes (NEC, mortality) were not assessed for growth outcomes. This included 6/26 (23%) in the formula group and 1/41 (2.4%) in the donor breast milk group, so potential bias 100% follow-up and low risk of bias for mortality and NEC
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Mead Johnson Nutrition

Lucas 1984a

Methods	Randomised controlled trial
Participants	159 infants of birth weight < 1850 g Stratified by birth weight < 1200 g and 1201 g to 1850 g

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Lucas 1984a *(Continued)*

	Infants with congenital abnormalities excluded. Infants with intrauterine growth restriction not excluded Study undertaken in the early 1980s in neonatal units in the Anglia region of the UK
Interventions	Preterm formula milk (N = 76) versus donor (mainly "drip") breast milk (N = 83) The formula was intended to be delivered at 180 mL/kg/day versus the breast milk at 200 mL/kg/day Feeds were assigned until the infant reached a weight of 2000 g or until discharge from the neonatal unit
Outcomes	Short-term outcomes: Time to regain birth weight (62 infants). Rates of change in weight (58 infants), crown-heel length (26 infants) and head circumference (48 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g Incidence of NEC - suspected and confirmed reported on complete cohort of 159 infants Longer-term outcomes: Validated neurological assessment at 18 months in 122 (85%) of surviving infants Bayley Mental Development Index and Psychomotor Development Index at 18 months post-term, in 114 (94%) of surviving infants suitable for the assessment Growth performance in surviving infants (weight, length and head circumference) at 9 months (110 infants), 18 months (136 infants) and 7.5 to 8 years (130 infants) post-term
Notes	The first "interim" report provided data on short-term growth outcomes in a predefined subset of the total cohort recruited. Follow-up at 18 months was achieved for more than 80% of surviving infants. Developmental assessments (Bayley Psychomotor and Mental Development Indices) at 18 months post-term were reported for 114 of the 159 children originally enrolled in the study. 16 children had died and 7 had been lost to follow-up. 12 surviving children had cerebral palsy affecting fine motor skills and these children were not assessed. A further 10 children were not assessed due to severe visual or hearing impairment or because follow-up data were obtained by telephone for geographical reasons.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced randomisation sequence was prepared for each centre, within strata defined by birth weight (method of sequence generation not stated explicitly)
Allocation concealment (selection bias)	Low risk	Sealed, numbered envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% assessment of in-hospital outcomes and > 80% follow-up for long-term outcomes (except for cognitive outcomes (verbal and performance intelligence quotient), which were assessed in about 20% of participants at ages 8 and 16 years)
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Farley Health Products

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Lucas 1984b

Methods	Randomised controlled trial
Participants	343 infants of birth weight < 1850 g. Stratified by birth weight < 1200 g and 1201 g to 1850 g. Infants with congenital abnormalities excluded. Infants with intrauterine growth restriction not excluded Study undertaken in the early 1980s in neonatal units in the Anglia region of the UK
Interventions	Preterm formula milk (N = 173) versus banked donor breast milk (N = 170) as a supplement to the mother's own breast milk
Outcomes	Short-term outcomes: time to regain birth weight (132 infants). Rates of change in weight (115 infants), crown-heel length (45 infants) and head circumference (97 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g Incidence of NEC - suspected and confirmed reported on complete cohort of 343 infants Longer-term outcomes: Validated neurological assessment, at 18 months, in 278 (88%) of surviving infants Bayley Mental Development Index and Psychomotor Development Index at 18 months, corrected for preterm gestation, in 273 (96%) of surviving infants suitable for the assessment Growth performance in surviving infants (weight, length and head circumference) at 9 months (259 infants), 18 months (302 infants) and 7.5 years to 8 years (290 infants) post-term
Notes	The first "interim" report provided data on short-term growth outcomes in a predefined subset of the total cohort recruited. Developmental assessments (Bayley Psychomotor and Mental Development Indices) at 18 months post-term were reported for 273 of 343 children originally enrolled in the study. 29 children had died and 12 had been lost to follow-up. 24 surviving children had cerebral palsy affecting fine motor skills and these children were not assessed. A further 5 children were not assessed due to severe visual or hearing impairment or because follow-up data were obtained by telephone for geographical reasons.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Sealed, numbered envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% assessment of in-hospital outcomes and > 80% follow-up for long-term outcomes except for cognitive outcomes (verbal and performance intelligence quotient) which were assessed in about 20% of participants at ages 8 and 16 years)
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Farley Health Products

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O'Connor 2016

Methods	Randomised controlled trial
Participants	363 VLBW infants whose mothers intended to breastfeed but whose own milk became insufficient from birth until 90 days of age or hospital discharge Four neonatal units in Ontario, Canada, 2010 to 2012
Interventions	Preterm formula (N = 182) versus donor breast milk (N = 181) given as a supplement to maternal breast milk (bovine-based multinutrient-fortified)
Outcomes	Cognitive composite score on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at 18 months post-term Bayley-III language and motor composite scores, mortality and morbidity index (late-onset infection, NEC (Bell stage ≥ II), chronic lung disease, or retinopathy of prematurity (treated medically or surgically), and growth during the feeding intervention
Notes	"A similar percentage of infants in the donor milk group (28.2%) and formula group (26.9%) were exclusively fed mother's milk". "Infants in both groups were fed substantial amounts of maternal milk, with approximately 25% in each group receiving only maternal milk, and the remainder receiving about 60% maternal milk".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-driven third-party randomisation service"
Allocation concealment (selection bias)	Low risk	Computer-randomised
Blinding (performance bias and detection bias) All outcomes	Low risk	Families and clinicians "blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 90% assessment for primary outcome
Selective reporting (reporting bias)	Low risk	No protocol deviations
Other bias	Unclear risk	Funded by the Canadian Institutes of Health Research (MOP No. 102638) and the Ontario Ministry of Health and Long-Term Care (grant No. 06465)

Raiha 1976

Methods	Randomised controlled trial
Participants	106 preterm infants of birth weight < 2100 g, but between 10th and 90th centiles for birth weight. Infants excluded if evidence of "physical abnormality or obvious disease" Premature Unit, Helsinki University Children's Hospital, 1972 to 1975
Interventions	Term formula milk (N = 84) versus unfortified donor breast milk (N = 22)

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Raiha 1976 *(Continued)*

	Feeds continued until a weight of 2.4 kg was attained or until infants were withdrawn from the study because of a "medical complication"
Outcomes	Time, from birth, to regain birth weight. Rate of weight gain from birth and from point of regained birth weight
Notes	Donor breast milk was given at a 170 mL/kg/day, compared with formula at 150 mL/kg/day, "in order to achieve equivalent calorie inputs". Donor breast milk-fed infants were given supplemental vitamins

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomly selected permutations of 1, 2, 3, 4 were prepared in advance, which were used to allocate to the 4 formula arms. Every 5th infant was assigned to pooled breast milk. Hence, it was not strictly random. Also, no details of how the permutations were generated
Allocation concealment (selection bias)	High risk	Every 5th infant was assigned to pooled breast milk so allocation concealment may have been suboptimal
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	95% follow-up (5/106 infants who were enrolled were dropped from the study for medical reasons)
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Wyeth Laboratories, the Juselius Foundation, and the New York State Department of Mental Hygiene

Schanler 2005

Methods	Randomised controlled trial
Participants	173 infants of gestational age < 30 weeks, whose mothers intended to breastfeed but whose own milk became insufficient from birth until 90 days of age or hospital discharge North Shore University Hospital, New York, USA, 2000 to 2003
Interventions	Preterm formula (N = 81) versus unfortified donor breast milk (N = 92) given as a supplement to maternal breast milk
Outcomes	Incidence of late-onset invasive infection and NEC, duration of hospitalisation and growth during the study period (weight gain, head circumference increment and length increment)
Notes	Participating infants received small quantities (20 mL/kg/day) of their own mother's milk during the first week after birth and continued for 3 to 5 days before the volume was advanced. Milk intake was increased by 20 mL/kg/day to 100 mL/kg/day at which time human milk fortifier was added. Subsequently the volume of fortified human milk was advanced by 20 mL/kg/day until 160 mL/kg/day was achieved. If no mother's milk was available and the baby was assigned to donor breast milk then a similar advancement and fortification protocol was followed. For all infants, adjustments in milk intake

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Schanler 2005 *(Continued)*

between 160 mL/kg/day and 200 mL/kg/day were recommended to ensure an average weekly weight gain of at least 15 g/kg per day.
17 enrolled infants were switched from donor breast milk to preterm formula because of poor weight gain but all of these analyses were by intention-to-treat. However, 7 infants who were never fed (3 in the donor milk group, 4 in the formula group) were excluded from the analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method not stated explicitly but very likely to be computer-generated since the random sequence was "an unbalanced blocked design, according to the stratification variables of gestational age and receipt of prenatal steroids"
Allocation concealment (selection bias)	Low risk	Allocation was "performed by the research nurse coordinator with sealed opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by the US National Institute of Child Health and Human Development and the National Institutes of Health General Clinical Research Center, Baylor College of Medicine, USA

Schultz 1980

Methods	Randomised controlled trial
Participants	20 preterm or LBW infants; all infants were "physically normal with no further signs of disease" Department of Paediatrics, University Medical School, Pecs, Hungary, prior to 1980
Interventions	Term formula milk (N = 10) versus donor breast milk (N = 10) for at least 4 weeks from birth
Outcomes	Time, from birth, to regain birth weight (mean but no SD reported) Mean weight gain from birth and from regaining birth weight calculable from graph but no SD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	No information given

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Schultz 1980 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder not stated

Tyson 1983

Methods	Randomised controlled trial
Participants	81 VLBW infants, excluding infants with "any significant illness" or those who required ventilatory support at day 10 Parklands Memorial Hospital, Dallas, USA, early 1980s
Interventions	Preterm formula milk (N = 44) versus donor breast milk (N = 37). The donor breast milk was not pasteurised. Feeds were allocated on the 10th day of life, and continued until the infant reached a weight of 2000 g or until withdrawn from the study because of "any illness requiring intravenous infusion of fat or protein".
Outcomes	Mean daily rates of change in weight, crown-heel length and head circumference from the 10th until the 30th day after birth
Notes	The feeds were not allocated until the 10th day after birth in order to avoid the use of protein-enriched formula "when active growth was unlikely". In the first 9 days of life the infants received a term formula or maternal expressed breast milk (if available). Although the report gave information on adverse outcomes, including NEC, the 5 affected infants were withdrawn from the study and not included in the analyses of growth rates.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Infants were stratified by birth weight and randomised, but how the sequence was generated is not stated
Allocation concealment (selection bias)	Low risk	Concealed envelope opened only after informed parental consent obtained
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five infants with adverse outcomes did not have growth data
Selective reporting (reporting bias)	Unclear risk	Protocol not available

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Tyson 1983 *(Continued)*

Other bias	Unclear risk	Funded by the Robert Wood Johnson Foundation, by the University of Texas Health Science Center at Dallas, and by a grant from Ross Laboratories

LBW: low birth weight
NEC: necrotising enterocolitis
SD: standard deviation
VLBW: very low birth weight

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

Study	Reason for exclusion
Brandstetter 2018	Development and proposal of a "decision tree" for prioritising donor breast milk use
Castellano 2019	Retrospective cohort study if impact of the availability of donor human milk
Colaizy 2015	Review article describing ongoing trials by authors, but without outcome data
Cooper 1984	Non-randomised study in preterm infants of feeding with formula or donor breast milk
Hair 2014	Randomised trial of human milk "cream" supplementation in very low birth weight infants
Jarvenpaa 1983	Non-randomised study comparing growth in low birth weight infants fed formula versus breast milk
Marseglia 2015	Randomised trial of a new preterm formula versus another formula, and a "reference" control group of infants fed with human milk based on maternal preference
Narayanan 1982	Comparative trial in low birth weight infants of feeding with formula milk versus "expressed human milk". Many of the infants were allocated to the human milk groups by preference rather than randomly
O'Connor 2003	Non-randomised study comparing growth, feeding tolerance, morbidity and development in low birth weight infants fed human milk or formula
Perrella 2015	Non-randomised study of gastric emptying rates in infants fed with fortified versus non-fortified human milk
Putet 1984	Non-randomised study of feeding very preterm infants with pooled human milk versus formula
Sullivan 2010	Randomised controlled trial of feeding very low birth weight infants with formula plus bovine milk-based fortifier versus donor human milk plus human milk-based fortifier; excluded because type of fortifier was cointervention
Svenningsen 1982	Randomised trial of two different formulas versus breast milk in low birth weight infants- most infants in the breast milk group received their own mother's expressed milk rather than donor breast milk (not randomised)
Tewari 2018	Randomised trial of early versus late feeding of very preterm infants with maternal or donor breast milk

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

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Perez 2015

Methods	Quasi-randomised controlled trial
Participants	200 low birth weight infants with insufficient maternal breast milk from birth to three weeks or until hospital discharge Neonatal units in San Carlos, Guatemala, 2012 to 2013
Interventions	Preterm formula (N = 100) versus donor breast milk (N = 100) given as a supplement to maternal breast milk (unfortified)
Outcomes	Growth parameters for three weeks Necrotising enterocolitis (unclear how defined)
Notes	Awaiting further information from authors regarding methods and findings

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

NCT01232725

Trial name or title	Donor human milk and neurodevelopmental outcomes in very low birthweight (VLBW) infants
Methods	Randomised controlled trial
Participants	121 very low birth weight infants Two neonatal units in USA (2009-15)
Interventions	Donor human milk (obtained from the Mother's Milk of Iowa), "fortified as appropriate" versus preterm formula
Outcomes	Primary: Bayley Scales of Infant Development, III scores (18 to 22 months' adjusted age)
Starting date	2009
Contact information	Tarah Colaizy: tarah-colaizy@uiowa.edu
Notes	Awaiting publication (preliminary data available from author but not yet sufficiently complete for inclusion) ClinicalTrials.gov Identifier: NCT01232725

NCT01390753

Trial name or title	Role of human milk bank in the protection of severe respiratory disease in very low birth weight premature infants
Methods	Randomised controlled trial
Participants	300 very low birth weight infants
Interventions	Donor breast milk and preterm formula versus preterm formula alone
Outcomes	Incidence of respiratory infections in infancy

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NCT01390753 *(Continued)*

Starting date	2012
Contact information	Fernando Pedro Polack: malinez@infant.org.ar
Notes	www.clinicaltrials.gov/ct2/show/NCT01390753

NCT01534481

Trial name or title	Donor milk vs. formula in extremely low birth weight (ELBW) infants (the MILK trial)
Methods	Randomised controlled trial
Participants	670 extremely low birth weight infants
Interventions	Donor breast milk (provided by the Human Milk Banking Association of North America) versus preterm formula
Outcomes	Primary: Bayley Scales of Infant Development III (BSID III) at 22 to 26 months post-term
Starting date	2012 (estimated completion 2018)
Contact information	Tarah Colaizy: tarah-colaizy@uiowa.edu
Notes	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) - sponsored in 17 centres, USA www.clinicaltrials.gov/ct2/show/NCT01534481?term=breast+milk&cond=weight&rank=5

NCT01686477

Trial name or title	PREterM FOrmula Or Donor breast milk for premature babies (PREMFOOD)
Methods	Randomised controlled trial (3 arms)
Participants	66 very preterm infants
Interventions	Donor breast milk or donor breast milk with fortifier or preterm formula
Outcomes	Primary: total body adiposity measured by magnetic resonance imaging (MRI) at "term equivalent"
Starting date	2012
Contact information	Luke Mills: l.mills@imperial.ac.uk
Notes	www.clinicaltrials.gov/ct2/show/NCT01686477

DATA AND ANALYSES

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Comparison 1. Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to regain birth weight (days from birth)	3	236	Mean Difference (IV, Fixed, 95% CI)	-3.08 [-4.38, -1.77]
1.1 Term formula versus unfortified DBM	2	166	Mean Difference (IV, Fixed, 95% CI)	-2.00 [-5.81, -2.18]
1.2 Preterm formula versus unfortified DBM	1	70	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-3.97, -0.23]
2 Weight gain (g/kg/day)	9	1028	Mean Difference (IV, Fixed, 95% CI)	2.51 [1.93, 3.08]
2.1 Term formula versus unfortified DBM	3	234	Mean Difference (IV, Fixed, 95% CI)	1.74 [0.96, 2.53]
2.2 Preterm formula versus unfortified DBM	3	249	Mean Difference (IV, Fixed, 95% CI)	4.16 [3.04, 5.28]
2.3 Preterm formula versus fortified DBM	3	545	Mean Difference (IV, Fixed, 95% CI)	2.37 [1.09, 3.65]
3 Linear growth (crown-heel length mm/week)	8	820	Mean Difference (IV, Fixed, 95% CI)	1.21 [0.77, 1.65]
3.1 Term formula versus unfortified DBM	2	128	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.10, 1.50]
3.2 Preterm formula versus unfortified DBM	3	147	Mean Difference (IV, Fixed, 95% CI)	1.96 [1.10, 2.82]
3.3 Preterm formula versus fortified DBM	3	545	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.33, 1.87]
4 Linear growth (crown-rump length mm/week)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Term formula versus unfortified DBM	1	106	Mean Difference (IV, Fixed, 95% CI)	0.59 [0.08, 1.10]
5 Linear growth (femoral length mm/week)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Term formula versus unfortified DBM	1	106	Mean Difference (IV, Fixed, 95% CI)	0.34 [0.13, 0.55]
6 Head growth (mm/week)	8	894	Mean Difference (IV, Fixed, 95% CI)	0.85 [0.47, 1.23]
6.1 Term formula versus unfortified DBM	2	128	Mean Difference (IV, Fixed, 95% CI)	0.81 [0.15, 1.47]
6.2 Preterm formula versus unfortified DBM	3	221	Mean Difference (IV, Fixed, 95% CI)	2.01 [1.21, 2.81]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Preterm formula versus fortified DBM	3	545	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.27, 0.86]
7 Weight (kg) at 9 months post-term	2	369	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.26, 0.21]
7.1 Preterm formula versus unfortified DBM	2	369	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.26, 0.21]
8 Length (cm) at 9 months post-term	2	369	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.64, 0.70]
8.1 Preterm formula versus unfortified DBM	2	369	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.64, 0.70]
9 Head circumference (cm) at 9 months post-term	2	369	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.13, 0.53]
9.1 Preterm formula versus unfortified DBM	2	369	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.13, 0.53]
10 Weight (kg) at 18 months post-term	2	438	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.15, 0.35]
10.1 Preterm formula versus unfortified DBM	2	438	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.15, 0.35]
11 Length (cm) at 18 months post-term	2	438	Mean Difference (IV, Fixed, 95% CI)	0.53 [-0.15, 1.20]
11.1 Preterm formula versus unfortified DBM	2	438	Mean Difference (IV, Fixed, 95% CI)	0.53 [-0.15, 1.20]
12 Head circumference (cm) at 18 months post-term	2	438	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.19, 0.39]
12.1 Preterm formula versus unfortified DBM	2	438	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.19, 0.39]
13 Weight (kg) at 7.5 to 8 years of age	2	420	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.42, 0.29]
13.1 Preterm formula versus unfortified DBM	2	420	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.42, 0.29]
14 Length (cm) at 7.5 to 8 years of age	2	420	Mean Difference (IV, Fixed, 95% CI)	0.05 [-1.12, 1.23]
14.1 Preterm formula versus unfortified DBM	2	420	Mean Difference (IV, Fixed, 95% CI)	0.05 [-1.12, 1.23]
15 Head circumference (cm) at 7.5 to 8 years of age	2	420	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.54, 0.16]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Preterm formula versus unfortified DBM	2	420	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.54, 0.16]
16 Bayley Mental Development Index at 18 months	2	387	Mean Difference (IV, Fixed, 95% CI)	1.24 [-2.62, 5.09]
16.1 Preterm formula versus unfortified DBM	2	387	Mean Difference (IV, Fixed, 95% CI)	1.24 [-2.62, 5.09]
17 Bayley Psychomotor Development Index at 18 months	2	387	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-3.43, 2.79]
17.1 Preterm formula versus unfortified DBM	2	387	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-3.43, 2.79]
18 Neurodevelopmental disability at 18 months	2	400	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.62, 2.35]
18.1 Preterm formula versus unfortified DBM	2	400	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.62, 2.35]
19 Bayley-III	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Cognitive	1	299	Mean Difference (IV, Fixed, 95% CI)	1.60 [-2.71, 5.91]
19.2 Language	1	299	Mean Difference (IV, Fixed, 95% CI)	3.0 [-2.01, 8.01]
19.3 Motor	1	299	Mean Difference (IV, Fixed, 95% CI)	2.20 [-2.07, 6.47]
20 Bayley-III score < 70	1	890	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.55, 1.11]
20.1 Cognitive	1	299	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.68]
20.2 Language	1	295	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.47, 1.30]
20.3 Motor	1	296	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.37, 1.44]
21 Cerebral palsy	1	299	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.21, 1.23]
22 Hearing impairment	1	299	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.30, 3.45]
23 Visual impairment	1	299	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 All-cause mortality	7	1527	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.80, 1.50]
24.1 Preterm formula versus unfortified DBM	3	572	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.70, 2.14]
24.2 Preterm formula versus fortified DBM	4	955	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.52]
25 Necrotising enterocolitis	9	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.23, 2.85]

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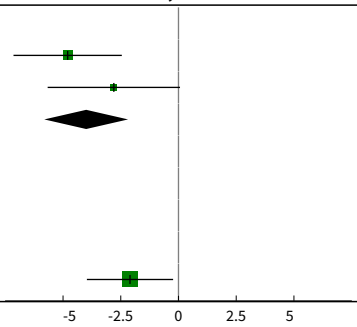
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Term formula versus unfortified DBM	1	67	Risk Ratio (M-H, Fixed, 95% CI)	4.73 [0.52, 43.09]
25.2 Preterm formula versus unfortified DBM	4	653	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [0.90, 9.87]
25.3 Preterm formula versus fortified DBM	4	955	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.03, 2.61]
26 Days after birth to establish full enteral feeding	2	123	Mean Difference (IV, Fixed, 95% CI)	0.33 [-2.57, 3.23]
26.1 Preterm formula versus unfortified DBM	1	70	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-3.66, 2.66]
26.2 Preterm formula versus fortified DBM	1	53	Mean Difference (IV, Fixed, 95% CI)	4.70 [-2.56, 11.96]
27 Feeding intolerance or diarrhoea	2	148	Risk Difference (M-H, Fixed, 95% CI)	0.10 [0.01, 0.19]
27.1 Term formula versus unfortified DBM	1	67	Risk Difference (M-H, Fixed, 95% CI)	0.21 [0.04, 0.38]
27.2 Preterm formula versus unfortified DBM	1	81	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.06, 0.10]
28 Invasive infection	5	1025	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.12]
28.1 Preterm formula versus unfortified DBM	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.08, 1.93]
28.2 Preterm formula versus fortified DBM	4	955	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.14]

Analysis 1.1. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 1 Time to regain birth weight (days from birth).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 Term formula versus unfortified DBM							
Gross 1983	20	10.3 (3.6)	40	15.1 (5.6)		30.79%	-4.8[-7.15,-2.45]
Raiha 1976	84	13.5 (5.3)	22	16.3 (6.3)		20.62%	-2.8[-5.67,0.07]
Subtotal ***	**104**		**62**			**51.41%**	**-4[-5.81,-2.18]**
Heterogeneity: Tau^2=0; Chi^2=1.12, df=1(P=0.29); I^2=10.74%							
Test for overall effect: Z=4.32(P<0.0001)							
1.1.2 Preterm formula versus unfortified DBM							
Costa 2018	35	12.9 (2.6)	35	15 (5)		48.59%	-2.1[-3.97,-0.23]



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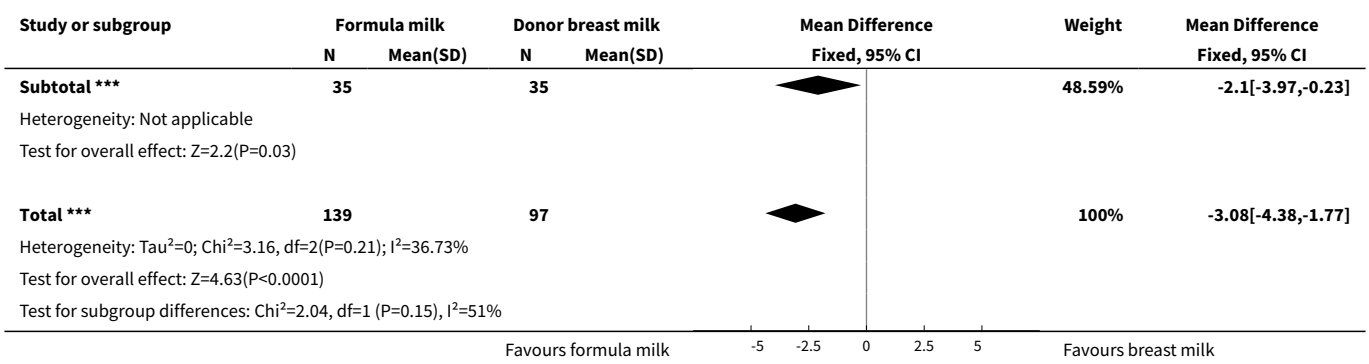
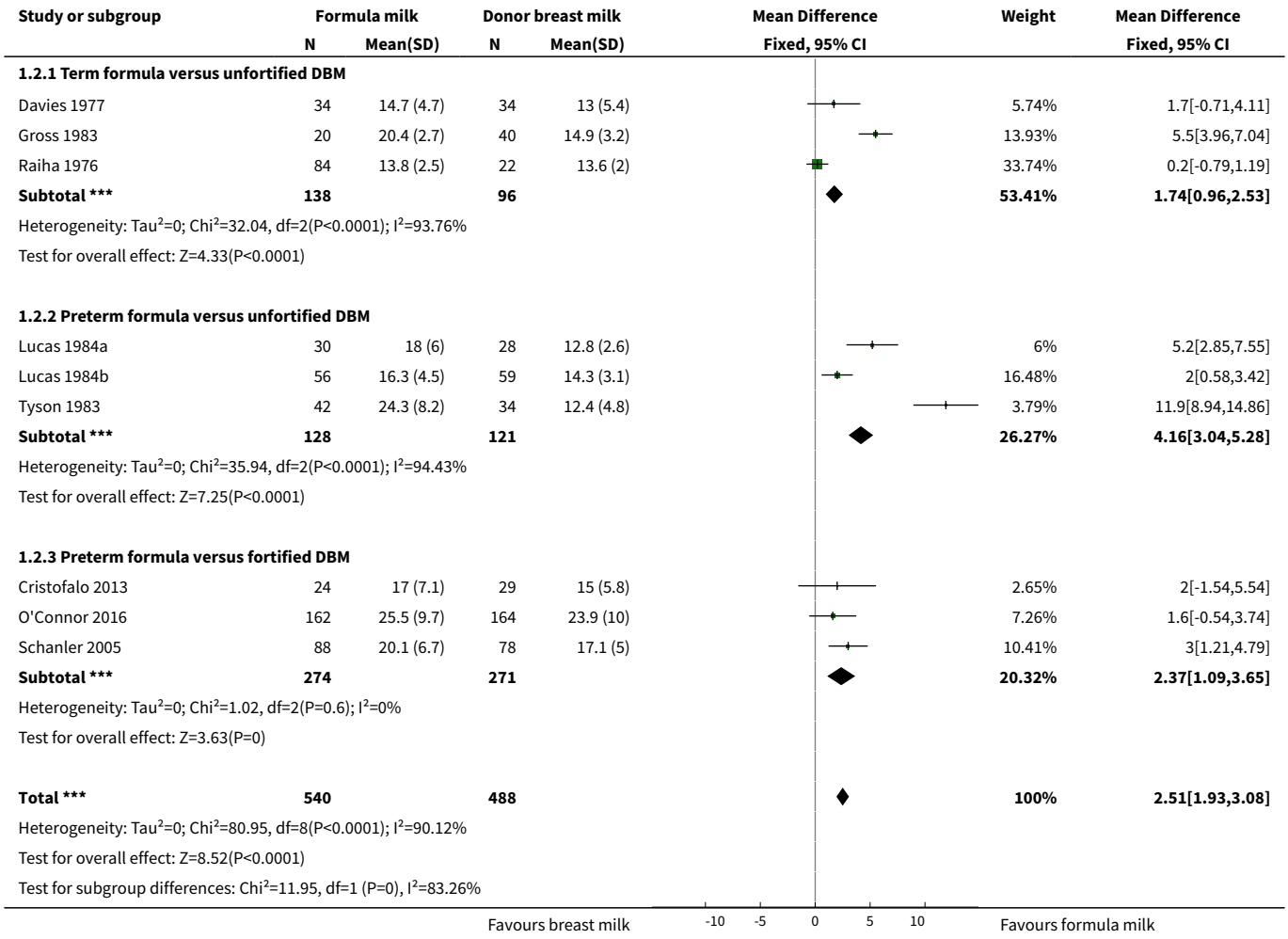


Analysis 1.2. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 2 Weight gain (g/kg/day).



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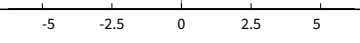
Analysis 1.3. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 3 Linear growth (crown-heel length mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.3.1 Term formula versus unfortified DBM							
Davies 1977	34	9.3 (2)	34	8.5 (2.4)		17.69%	0.8[-0.25,1.85]
Gross 1983	20	7.2 (1.8)	40	6.4 (1.6)		22.47%	0.8[-0.13,1.73]
Subtotal ***	**54**		**74**			**40.17%**	**0.8[0.1,1.5]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Z=2.25(P=0.02)							
1.3.2 Preterm formula versus unfortified DBM							
Lucas 1984a	12	9.7 (2.2)	14	7.3 (2.4)		6.23%	2.4[0.63,4.17]
Lucas 1984b	20	9.6 (2.2)	25	8.4 (1.4)		15.85%	1.2[0.09,2.31]
Tyson 1983	42	11 (4)	34	7 (5)		4.55%	4[1.93,6.07]
Subtotal ***	**74**		**73**			**26.64%**	**1.96[1.1,2.82]**
Heterogeneity: Tau²=0; Chi²=5.77, df=2(P=0.06); I²=65.33%							
Test for overall effect: Z=4.49(P<0.0001)							
1.3.3 Preterm formula versus fortified DBM							
Cristofalo 2013	24	11.2 (2.8)	29	8.4 (2.1)		10.61%	2.8[1.44,4.16]
O'Connor 2016	162	10.7 (4.6)	164	10.1 (4.5)		19.99%	0.6[-0.39,1.59]
Schanler 2005	88	10 (10)	78	12 (8)		2.6%	-2[-4.74,0.74]
Subtotal ***	**274**		**271**			**33.19%**	**1.1[0.33,1.87]**
Heterogeneity: Tau²=0; Chi²=11.93, df=2(P=0); I²=83.24%							
Test for overall effect: Z=2.81(P=0)							
Total ***	**402**		**418**			**100%**	**1.21[0.77,1.65]**
Heterogeneity: Tau²=0; Chi²=22.05, df=7(P=0); I²=68.26%							
Test for overall effect: Z=5.36(P<0.0001)							
Test for subgroup differences: Chi²=4.35, df=1 (P=0.11), I²=54.04%							



Favours breast milk — Favours formula milk

Analysis 1.4. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 4 Linear growth (crown-rump length mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.4.1 Term formula versus unfortified DBM							
Raiha 1976	84	5.3 (1.8)	22	4.8 (0.8)		100%	0.59[0.08,1.1]
Subtotal ***	**84**		**22**			**100%**	**0.59[0.08,1.1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.25(P=0.02)							

Favours breast milk — Favours formula milk

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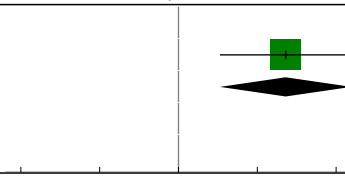
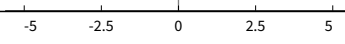
Analysis 1.5. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 5 Linear growth (femoral length mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Term formula versus unfortified DBM							
Raiha 1976	84	2 (0.5)	22	1.6 (0.4)		100%	0.34[0.13,0.55]
Subtotal ***	**84**		**22**			**100%**	**0.34[0.13,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.2(P=0)							



Analysis 1.6. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 6 Head growth (mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 Term formula versus unfortified DBM							
Davies 1977	34	7.4 (1.6)	34	6.8 (2)		19.29%	0.6[-0.26,1.46]
Gross 1983	20	8.8 (2.2)	40	7.7 (1.1)		13.67%	1.1[0.08,2.12]
Subtotal ***	**54**		**74**			**32.95%**	**0.81[0.15,1.47]**
Heterogeneity: Tau^2=0; Chi^2=0.54, df=1(P=0.46); I^2=0%							
Test for overall effect: Z=2.4(P=0.02)							
1.6.2 Preterm formula versus unfortified DBM							
Lucas 1984a	25	11 (3.6)	23	8.6 (2.7)		4.45%	2.4[0.61,4.19]
Lucas 1984b	43	10.1 (2.9)	54	9.4 (2.7)		11.26%	0.7[-0.43,1.83]
Tyson 1983	42	12 (2)	34	8 (4)		6.58%	4[2.53,5.47]
Subtotal ***	**110**		**111**			**22.29%**	**2.01[1.21,2.81]**
Heterogeneity: Tau^2=0; Chi^2=12.37, df=2(P=0); I^2=83.83%							
Test for overall effect: Z=4.93(P<0.0001)							
1.6.3 Preterm formula versus fortified DBM							
Cristofalo 2013	24	8.8 (1.8)	29	7.8 (2.6)		10.11%	1[-0.19,2.19]
O'Connor 2016	162	8.3 (2.9)	164	8.2 (3.2)		32.54%	0.1[-0.56,0.76]
Schanler 2005	88	9 (8)	78	9 (9)		2.11%	0[-2.6,2.6]
Subtotal ***	**274**		**271**			**44.76%**	**0.3[-0.27,0.86]**
Heterogeneity: Tau^2=0; Chi^2=1.73, df=2(P=0.42); I^2=0%							
Test for overall effect: Z=1.04(P=0.3)							
Total ***	**438**		**456**			**100%**	**0.85[0.47,1.23]**
Heterogeneity: Tau^2=0; Chi^2=26.42, df=7(P=0); I^2=73.51%							
Test for overall effect: Z=4.4(P<0.0001)							
Test for subgroup differences: Chi^2=11.78, df=1 (P=0), I^2=83.02%							



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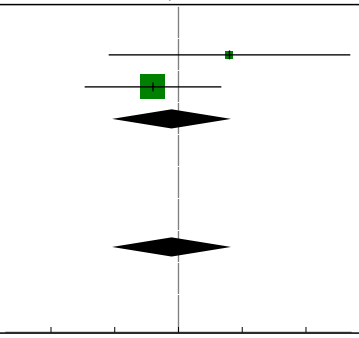
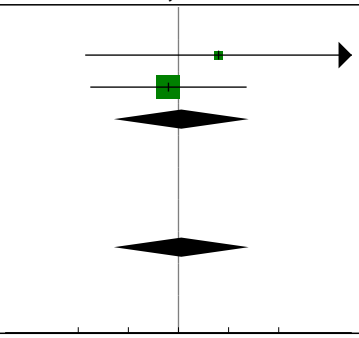
Analysis 1.7. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 7 Weight (kg) at 9 months post-term.

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 Preterm formula versus unfortified DBM							
Lucas 1984a	48	7.9 (1.3)	62	7.7 (1.2)		24.24%	0.2[-0.27,0.67]
Lucas 1984b	126	7.9 (1.1)	133	8 (1.1)		75.76%	-0.1[-0.37,0.17]
Subtotal ***	**174**		**195**			**100%**	**-0.03[-0.26,0.21]**
Heterogeneity: Tau^2=0; Chi^2=1.17, df=1(P=0.28); I^2=14.29%							
Test for overall effect: Z=0.23(P=0.82)							
Total ***	**174**		**195**			**100%**	**-0.03[-0.26,0.21]**
Heterogeneity: Tau^2=0; Chi^2=1.17, df=1(P=0.28); I^2=14.29%							
Test for overall effect: Z=0.23(P=0.82)							



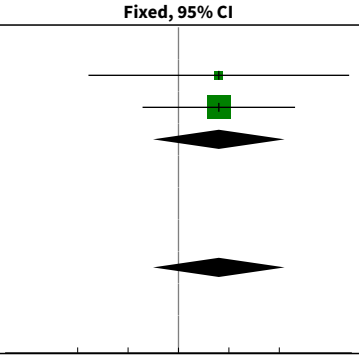
Analysis 1.8. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 8 Length (cm) at 9 months post-term.

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.8.1 Preterm formula versus unfortified DBM							
Lucas 1984a	48	69.2 (3.7)	62	68.8 (3.3)		25.56%	0.4[-0.93,1.73]
Lucas 1984b	126	69.4 (3.2)	133	69.5 (3.2)		74.44%	-0.1[-0.88,0.68]
Subtotal ***	**174**		**195**			**100%**	**0.03[-0.64,0.7]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=0.08(P=0.94)							
Total ***	**174**		**195**			**100%**	**0.03[-0.64,0.7]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=0.08(P=0.94)							



Analysis 1.9. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 9 Head circumference (cm) at 9 months post-term.

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.9.1 Preterm formula versus unfortified DBM							
Lucas 1984a	48	45.3 (1.8)	62	45.1 (1.6)		25.5%	0.2[-0.45,0.85]
Lucas 1984b	126	45.7 (1.6)	133	45.5 (1.5)		74.5%	0.2[-0.18,0.58]
Subtotal ***	**174**		**195**			**100%**	**0.2[-0.13,0.53]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Z=1.2(P=0.23)							
Total ***	**174**		**195**			**100%**	**0.2[-0.13,0.53]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Z=1.2(P=0.23)							



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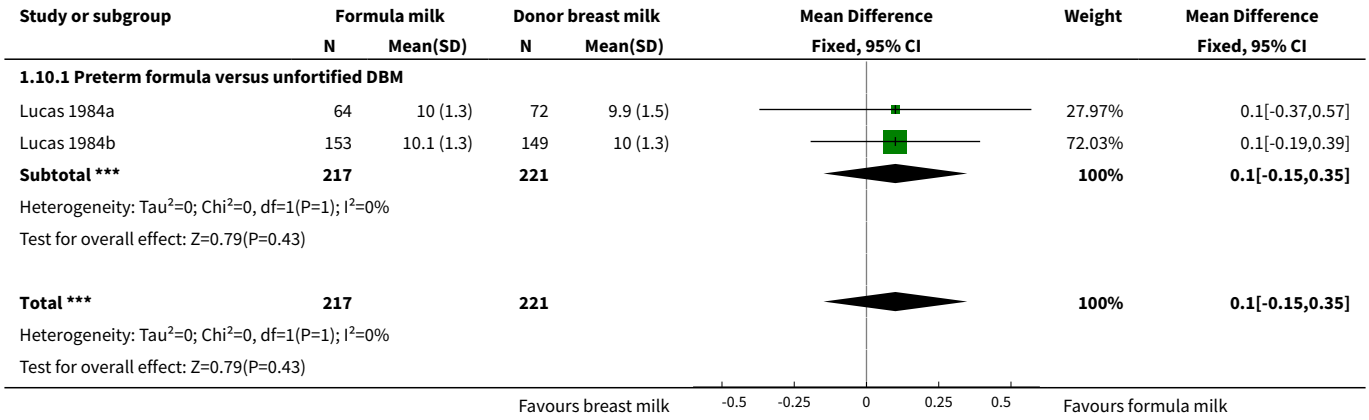
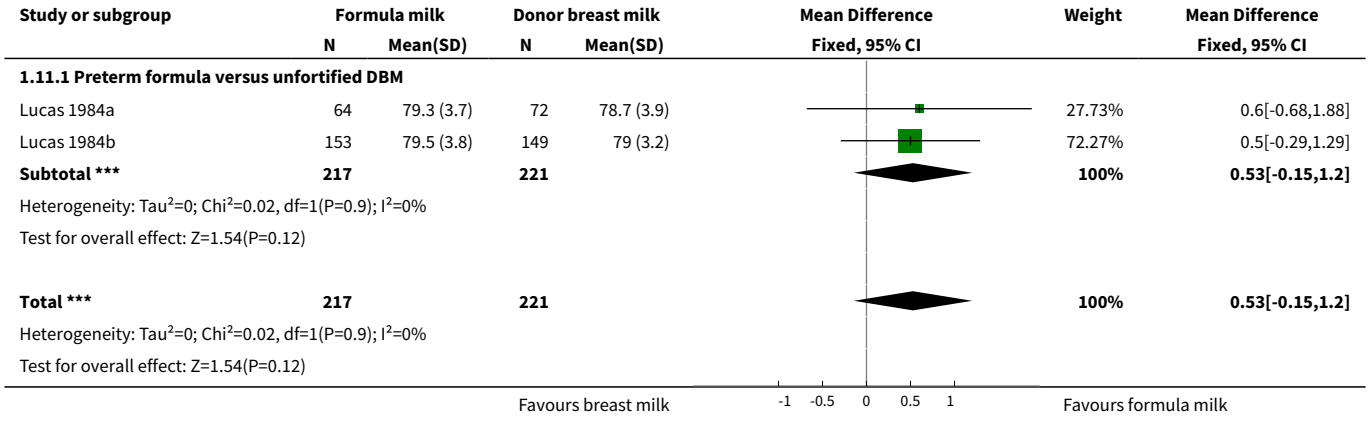
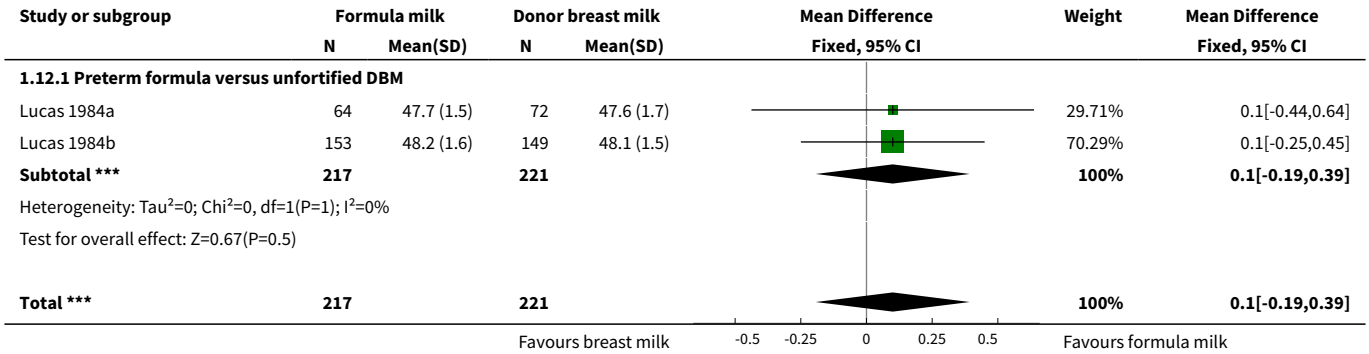
Analysis 1.10. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 10 Weight (kg) at 18 months post-term.



Analysis 1.11. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 11 Length (cm) at 18 months post-term.



Analysis 1.12. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 12 Head circumference (cm) at 18 months post-term.



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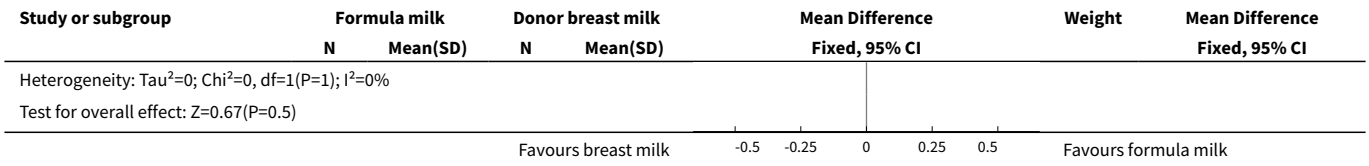
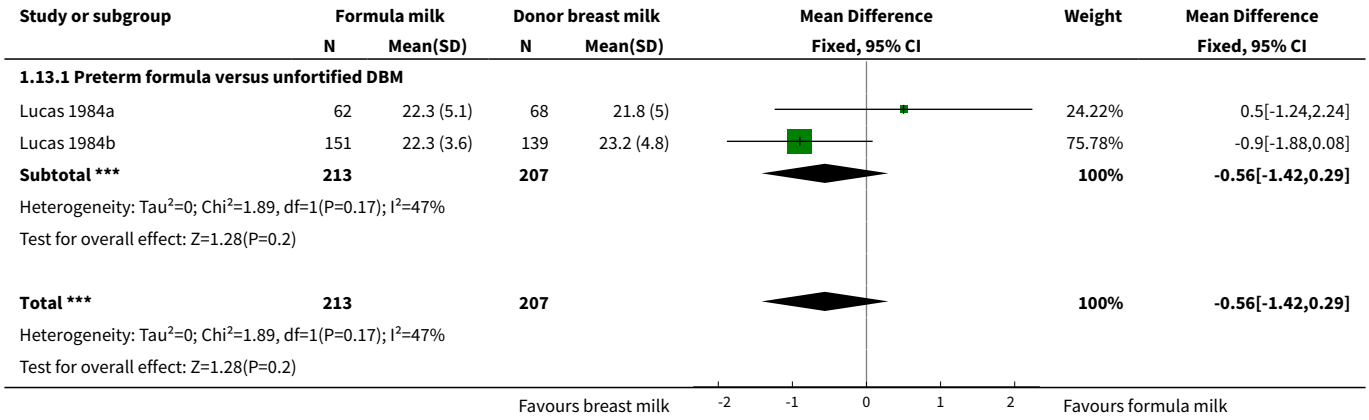
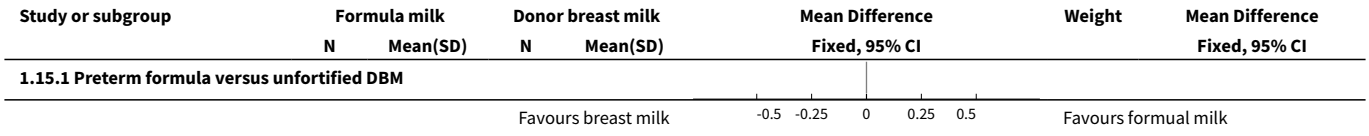


Analysis 1.13. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 13 Weight (kg) at 7.5 to 8 years of age.



Analysis 1.14. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 14 Length (cm) at 7.5 to 8 years of age.

Analysis 1.15. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 15 Head circumference (cm) at 7.5 to 8 years of age.



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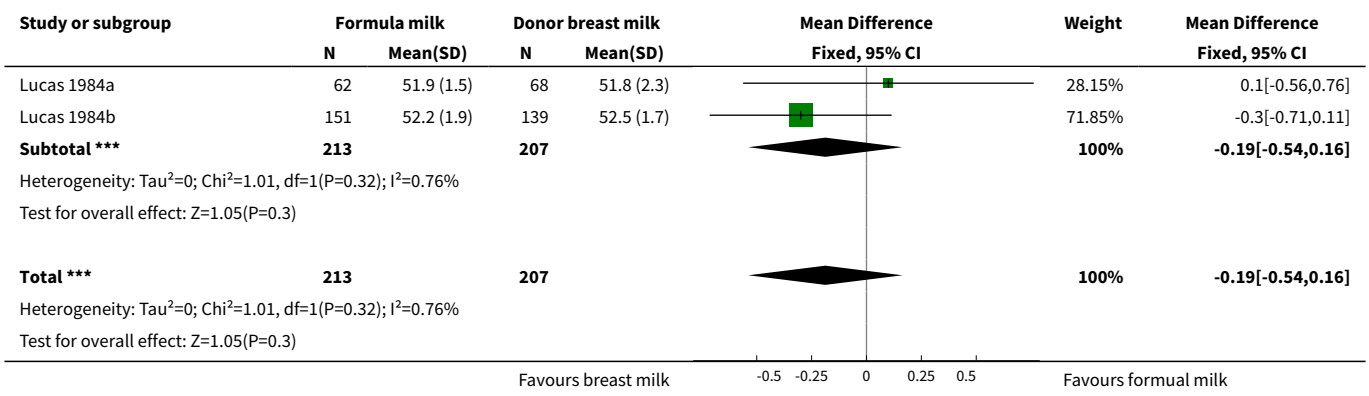
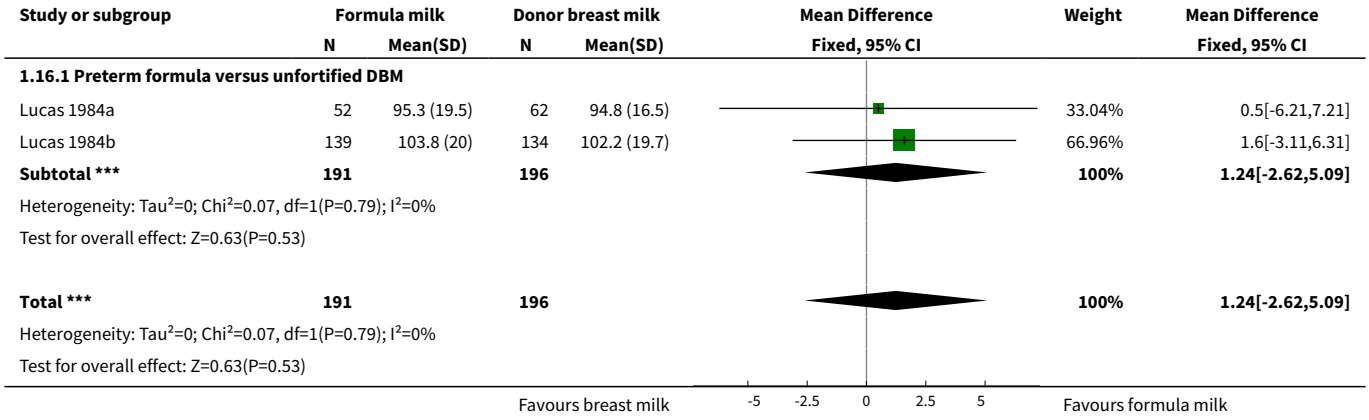
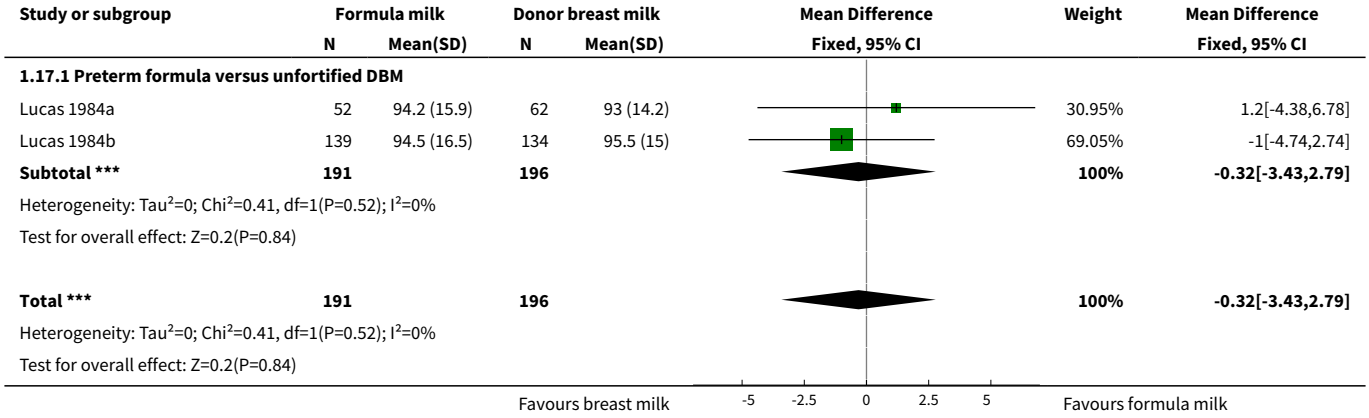


Analysis 1.16. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 16 Bayley Mental Development Index at 18 months.



Analysis 1.17. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 17 Bayley Psychomotor Development Index at 18 months.



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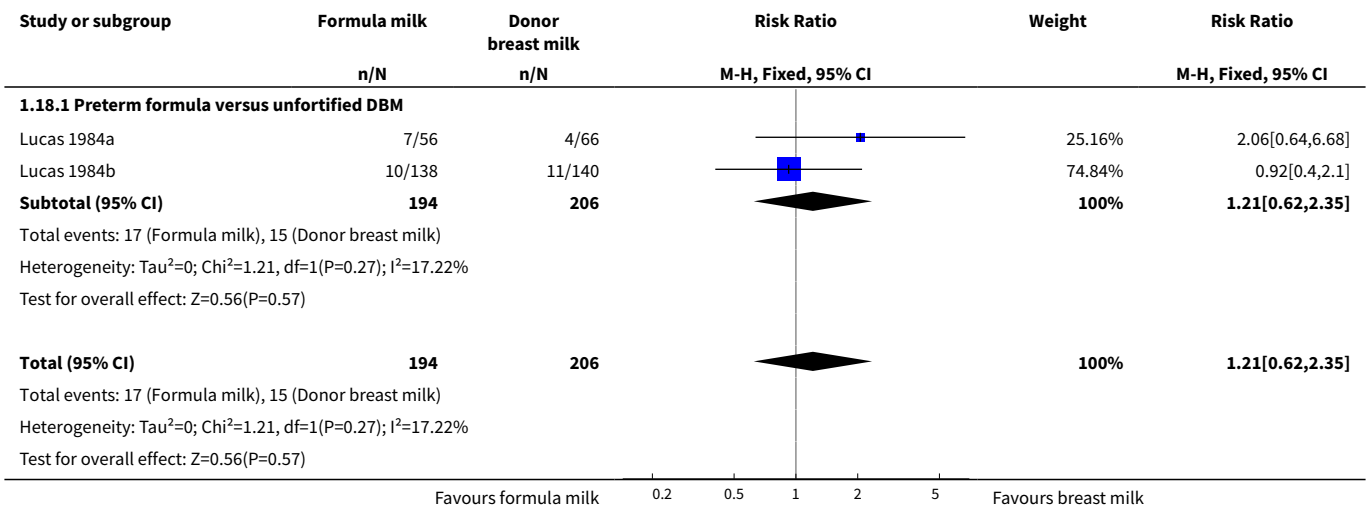
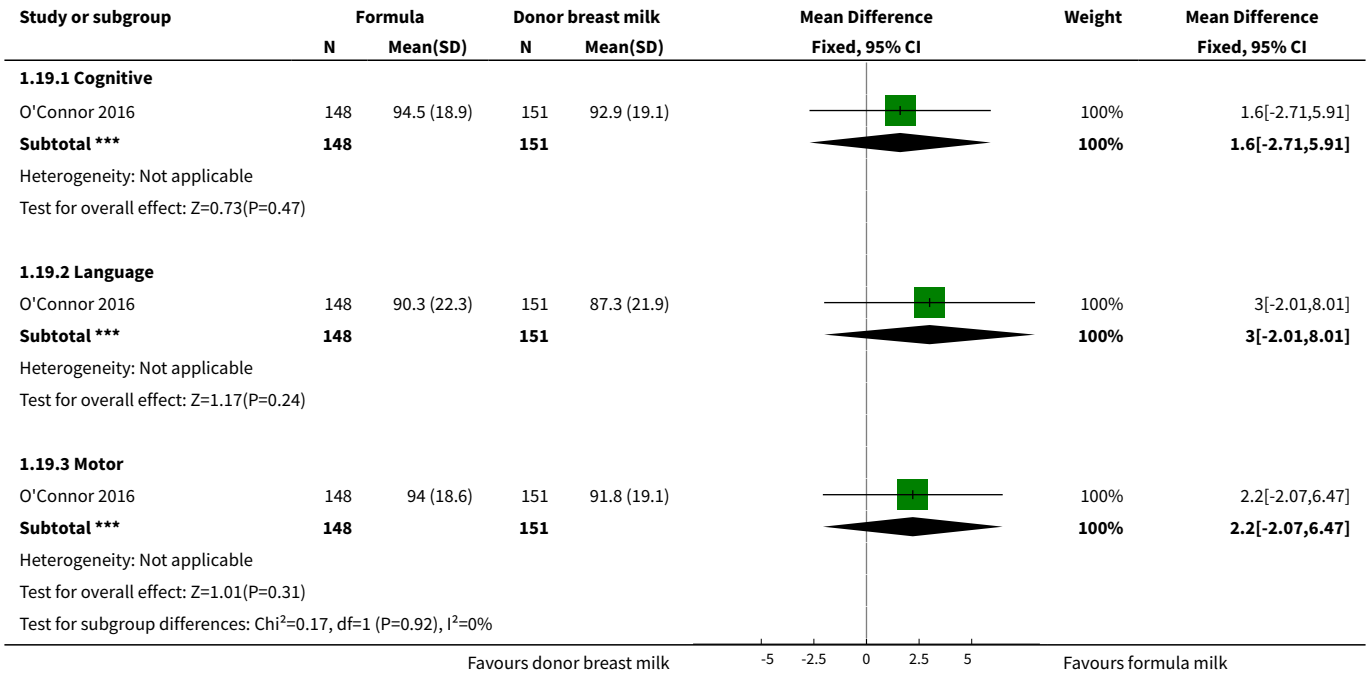
Analysis 1.18. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 18 Neurodevelopmental disability at 18 months.



Analysis 1.19. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 19 Bayley-III.



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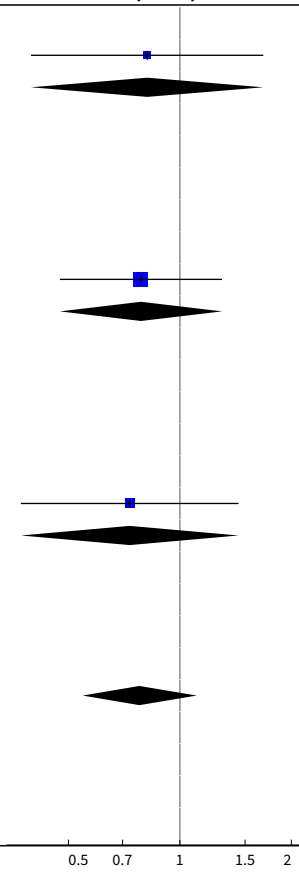
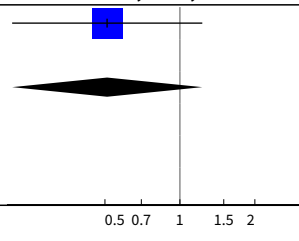
Analysis 1.20. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 20 Bayley-III score < 70.

Study or subgroup	Formula milk n/N	Donor breast milk n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Cognitive					
O'Connor 2016	12/148	15/151		24.25%	0.82[0.4,1.68]
Subtotal (95% CI)	**148**	**151**		**24.25%**	**0.82[0.4,1.68]**
Total events: 12 (Formula milk), 15 (Donor breast milk)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.55(P=0.58)					
1.20.2 Language					
O'Connor 2016	22/145	29/150		46.55%	0.78[0.47,1.3]
Subtotal (95% CI)	**145**	**150**		**46.55%**	**0.78[0.47,1.3]**
Total events: 22 (Formula milk), 29 (Donor breast milk)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
1.20.3 Motor					
O'Connor 2016	13/147	18/149		29.2%	0.73[0.37,1.44]
Subtotal (95% CI)	**147**	**149**		**29.2%**	**0.73[0.37,1.44]**
Total events: 13 (Formula milk), 18 (Donor breast milk)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.9(P=0.37)					
Total (95% CI)	**440**	**450**		**100%**	**0.78[0.55,1.11]**
Total events: 47 (Formula milk), 62 (Donor breast milk)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=1.4(P=0.16)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.98), I^2=0%					



Analysis 1.21. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 21 Cerebral palsy.

Study or subgroup	Formula milk n/N	Donor breast milk n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
O'Connor 2016	7/148	14/151		100%	0.51[0.21,1.23]
Total (95% CI)	**148**	**151**		**100%**	**0.51[0.21,1.23]**
Total events: 7 (Formula milk), 14 (Donor breast milk)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					



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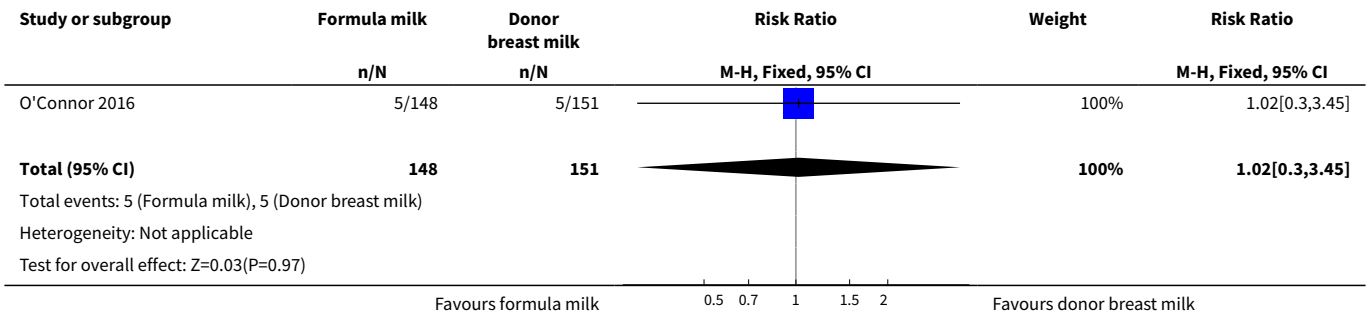
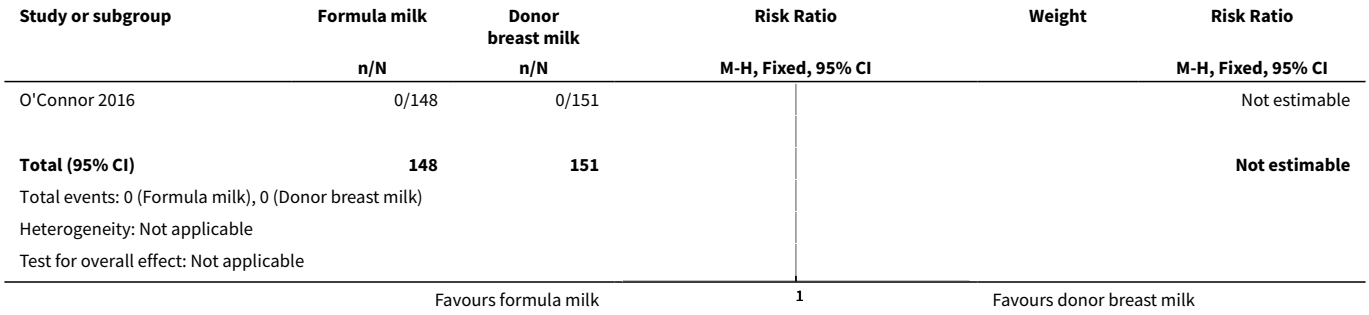
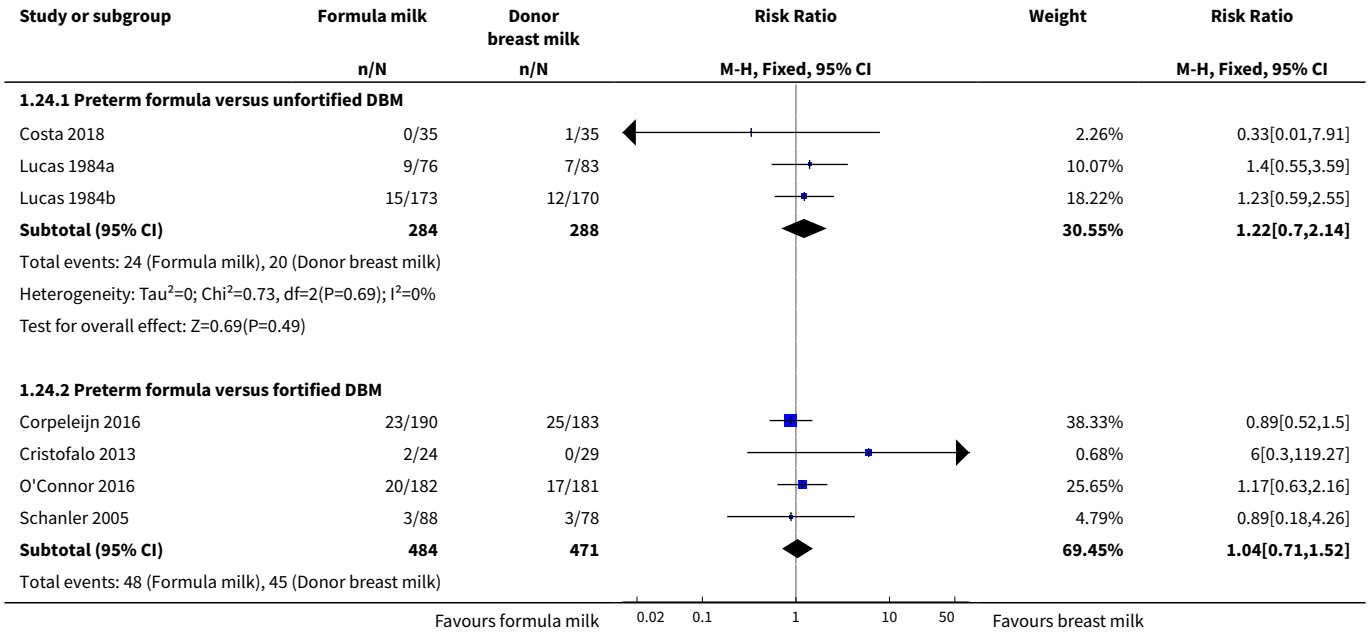
Analysis 1.22. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 22 Hearing impairment.



Analysis 1.23. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 23 Visual impairment.



Analysis 1.24. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 24 All-cause mortality.



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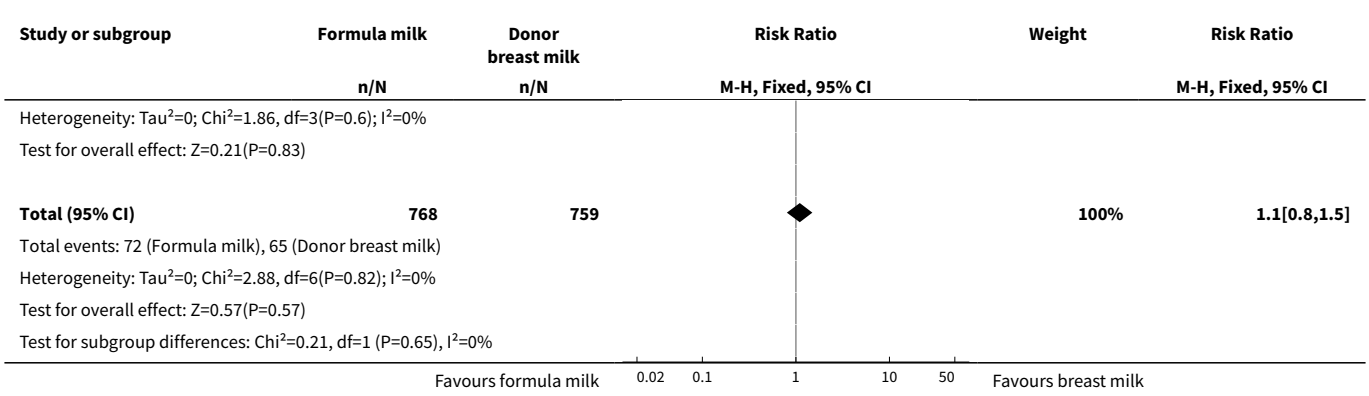
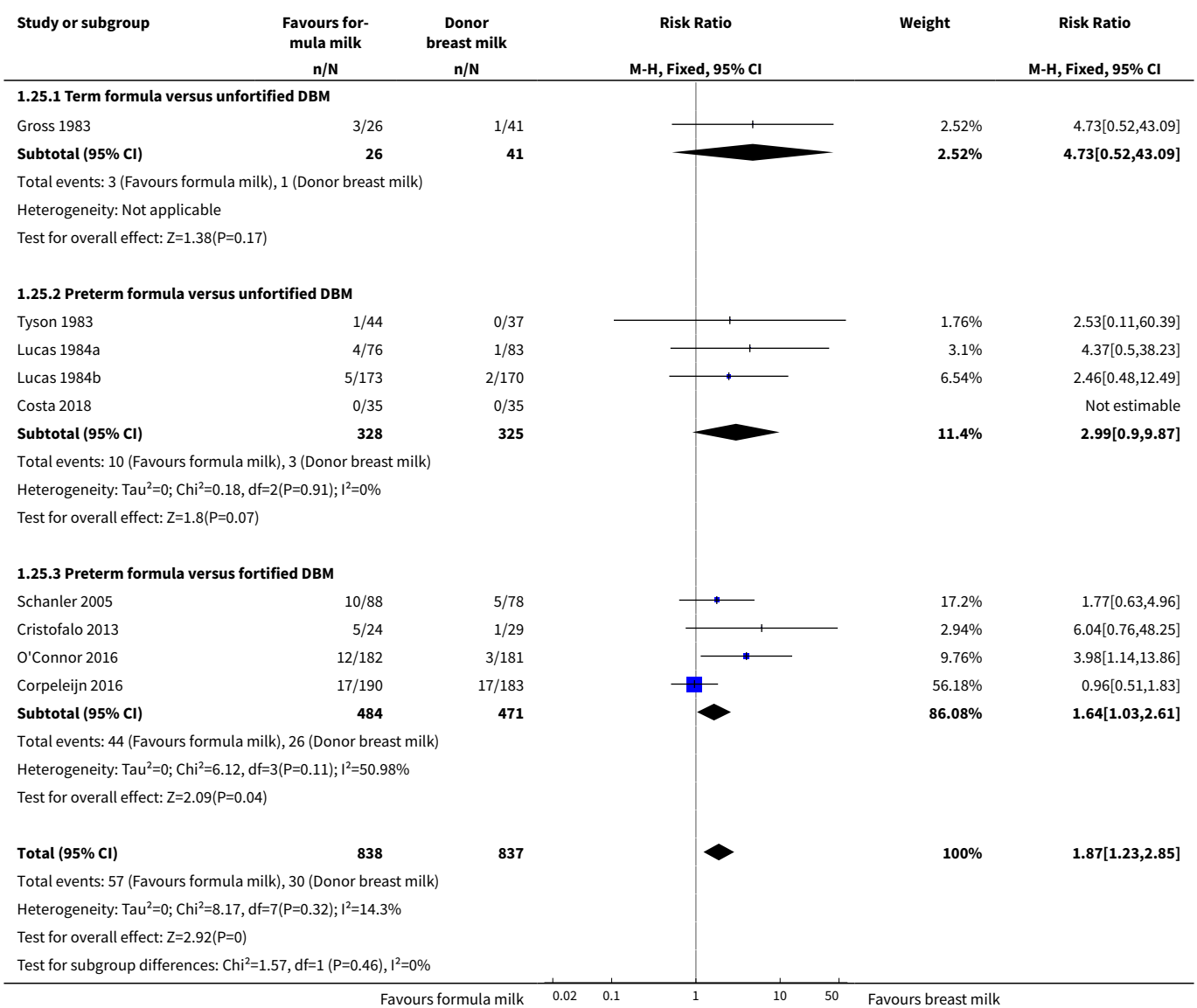


Analysis 1.25. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 25 Necrotising enterocolitis.



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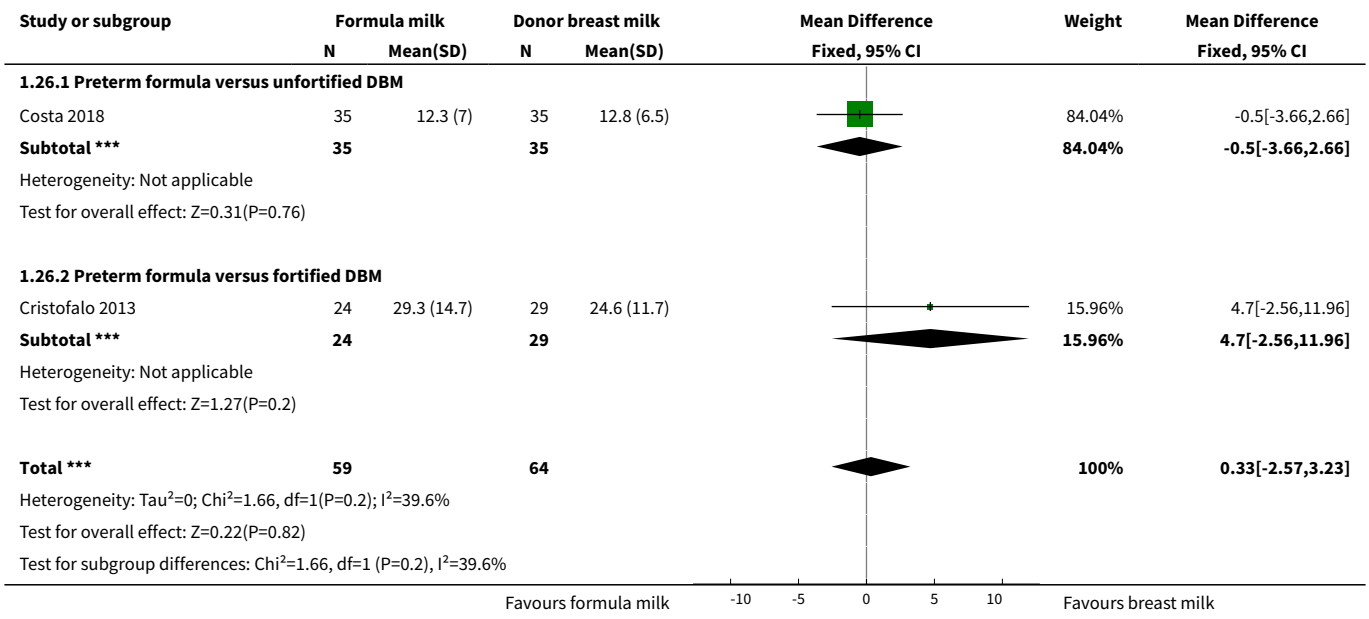
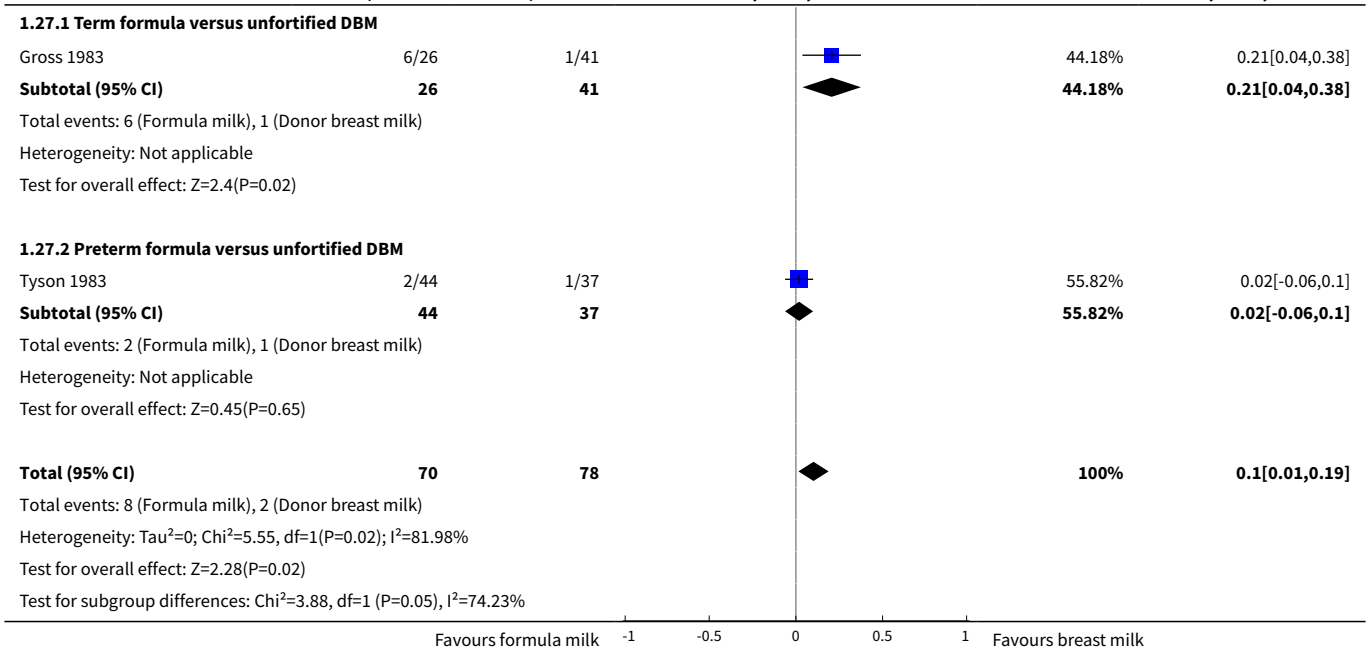
Analysis 1.26. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 26 Days after birth to establish full enteral feeding.



Analysis 1.27. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 27 Feeding intolerance or diarrhoea.



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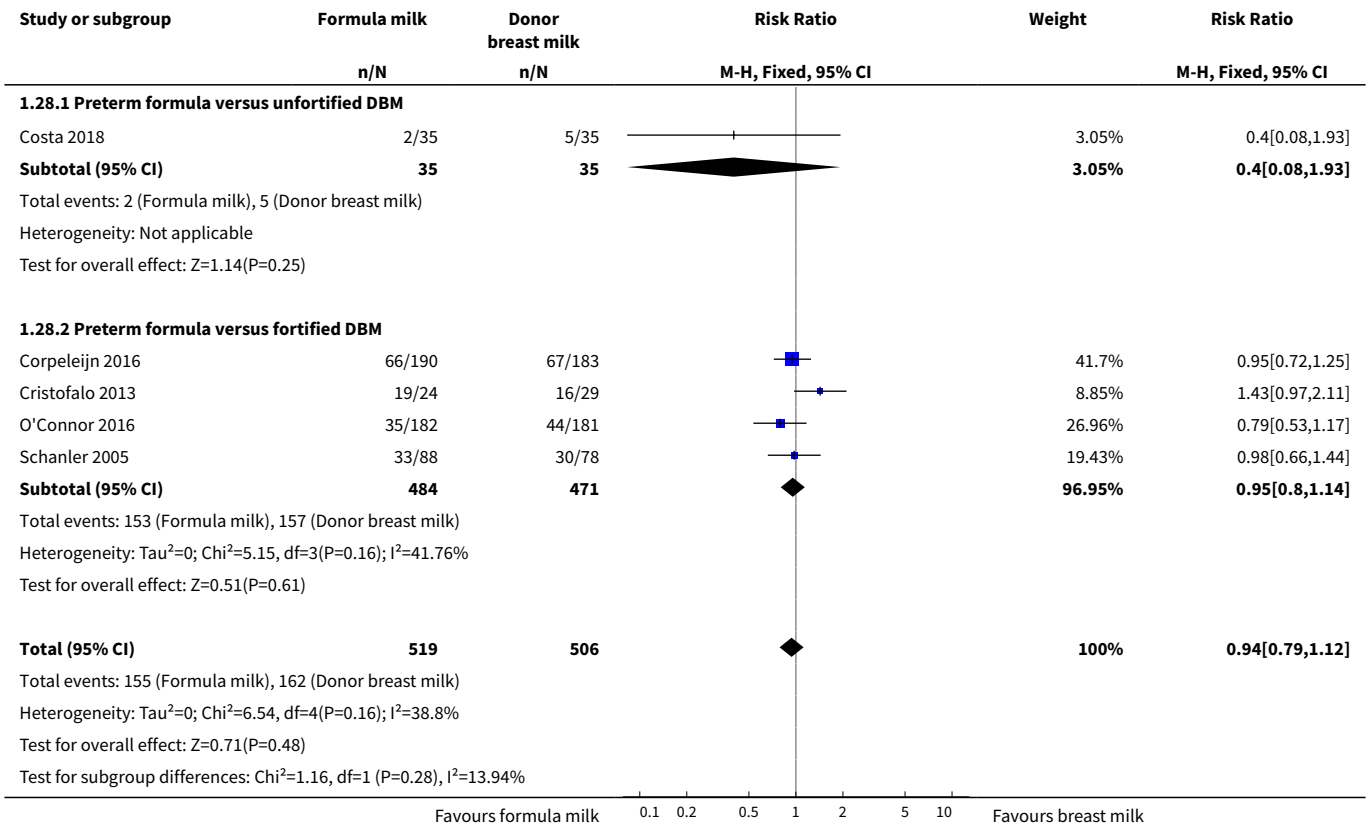
Analysis 1.28. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 28 Invasive infection.



Comparison 2. Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Weight gain (g/kg/day)	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Sole diet	6	421	Mean Difference (IV, Fixed, 95% CI)	2.65 [1.94, 3.36]
1.2 Supplement	3	607	Mean Difference (IV, Fixed, 95% CI)	2.22 [1.23, 3.21]
2 Linear growth (crown-heel length mm/week)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Sole diet	5	283	Mean Difference (IV, Fixed, 95% CI)	1.54 [0.98, 2.11]
2.2 Supplement	3	537	Mean Difference (IV, Fixed, 95% CI)	0.67 [-0.04, 1.38]
3 Head growth (mm/week)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Sole diet	5	305	Mean Difference (IV, Fixed, 95% CI)	1.36 [0.85, 1.88]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.2 Supplement	3	589	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.32, 0.80]
4 Weight (kg) at 9 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Sole diet	1	110	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.27, 0.67]
4.2 Supplement	1	259	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.37, 0.17]
5 Length (cm) at 9 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Sole diet	1	110	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.93, 1.73]
5.2 Supplement	1	259	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.88, 0.68]
6 Head circumference (cm) at 9 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Sole diet	1	110	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.45, 0.85]
6.2 Supplement	1	259	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.18, 0.58]
7 Weight (kg) at 18 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Sole diet	1	136	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.37, 0.57]
7.2 Supplement	1	302	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.19, 0.39]
8 Length (cm) at 18 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Sole diet	1	136	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.68, 1.88]
8.2 Supplement	1	302	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.29, 1.29]
9 Head circumference (cm) at 18 months post-term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Sole diet	1	136	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.44, 0.64]
9.2 Supplement	1	302	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.25, 0.45]
10 Weight (kg) at 7.5 to 8 years of age	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Sole diet	1	130	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.24, 2.24]
10.2 Supplement	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.88, 0.08]
11 Length (cm) at 7.5 to 8 years of age	2	420	Mean Difference (IV, Fixed, 95% CI)	0.05 [-1.12, 1.23]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Sole diet	1	130	Mean Difference (IV, Fixed, 95% CI)	1.0 [-1.26, 3.26]
11.2 Supplement	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.68, 1.08]
12 Head circumference (cm) at 7.5 to 8 years of age	2	420	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.54, 0.16]
12.1 Sole diet	1	130	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.56, 0.76]
12.2 Supplement	1	290	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.71, 0.11]
13 Bayley Mental Development Index at 18 months	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Sole diet	1	114	Mean Difference (IV, Fixed, 95% CI)	0.5 [-6.21, 7.21]
13.2 Supplement	1	273	Mean Difference (IV, Fixed, 95% CI)	1.60 [-3.11, 6.31]
14 Bayley Psychomotor Development Index at 18 months	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Sole diet	1	114	Mean Difference (IV, Fixed, 95% CI)	1.20 [-4.38, 6.78]
14.2 Supplement	1	273	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-4.74, 2.74]
15 Neurodevelopmental disability at 18 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Sole diet	1	122	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.64, 6.68]
15.2 Supplement	1	278	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.40, 2.10]
16 All-cause mortality	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Sole diet	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.71, 4.07]
16.2 Supplement	5	1315	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.73, 1.44]
17 Necrotising enterocolitis	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Sole diet	4	360	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [1.47, 14.56]
17.2 Supplement	5	1315	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.98, 2.47]
18 Incidence of invasive infection	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Sole diet	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.97, 2.11]
18.2 Supplement	4	972	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.08]

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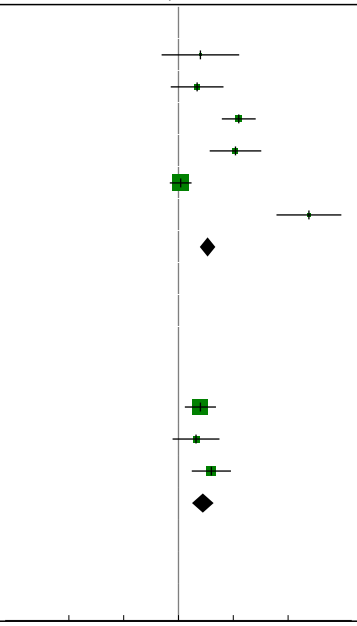
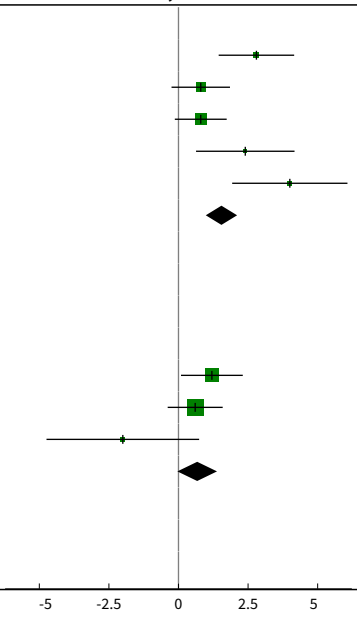
Analysis 2.1. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 1 Weight gain (g/kg/day).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Sole diet							
Cristofalo 2013	24	17 (7.1)	29	15 (5.8)		4.03%	2[-1.54,5.54]
Davies 1977	34	14.7 (4.7)	34	13 (5.4)		8.71%	1.7[-0.71,4.11]
Gross 1983	20	20.4 (2.7)	40	14.9 (3.2)		21.16%	5.5[3.96,7.04]
Lucas 1984a	30	18 (6)	28	12.8 (2.6)		9.11%	5.2[2.85,7.55]
Raiha 1976	84	13.8 (2.5)	22	13.6 (2)		51.24%	0.2[-0.79,1.19]
Tyson 1983	42	24.3 (8.2)	34	12.4 (4.8)		5.76%	11.9[8.94,14.86]
Subtotal ***	**234**		**187**			**100%**	**2.65[1.94,3.36]**
Heterogeneity: Tau²=0; Chi²=79.31, df=5(P<0.0001); I²=93.7%							
Test for overall effect: Z=7.32(P<0.0001)							
2.1.2 Supplement							
Lucas 1984b	56	16.3 (4.5)	59	14.3 (3.1)		48.26%	2[0.58,3.42]
O'Connor 2016	162	25.5 (9.7)	164	23.9 (10)		21.26%	1.6[-0.54,3.74]
Schanler 2005	88	20.1 (6.7)	78	17.1 (5)		30.48%	3[1.21,4.79]
Subtotal ***	**306**		**301**			**100%**	**2.22[1.23,3.21]**
Heterogeneity: Tau²=0; Chi²=1.15, df=2(P=0.56); I²=0%							
Test for overall effect: Z=4.41(P<0.0001)							
Test for subgroup differences: Chi²=0.49, df=1 (P=0.48), I²=0%							



Analysis 2.2. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 2 Linear growth (crown-heel length mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.2.1 Sole diet							
Cristofalo 2013	24	11.2 (2.8)	29	8.4 (2.1)		17.23%	2.8[1.44,4.16]
Davies 1977	34	9.3 (2)	34	8.5 (2.4)		28.74%	0.8[-0.25,1.85]
Gross 1983	20	7.2 (1.8)	40	6.4 (1.6)		36.51%	0.8[-0.13,1.73]
Lucas 1984a	12	9.7 (2.2)	14	7.3 (2.4)		10.13%	2.4[0.63,4.17]
Tyson 1983	42	11 (4)	34	7 (5)		7.39%	4[1.93,6.07]
Subtotal ***	**132**		**151**			**100%**	**1.54[0.98,2.11]**
Heterogeneity: Tau²=0; Chi²=13.98, df=4(P=0.01); I²=71.38%							
Test for overall effect: Z=5.37(P<0.0001)							
2.2.2 Supplement							
Lucas 1984b	20	9.6 (2.2)	25	8.4 (1.4)		41.24%	1.2[0.09,2.31]
O'Connor 2016	162	10.7 (4.6)	164	10.1 (4.5)		52%	0.6[-0.39,1.59]
Schanler 2005	88	10 (10)	78	12 (8)		6.75%	-2[-4.74,0.74]
Subtotal ***	**270**		**267**			**100%**	**0.67[-0.04,1.38]**
Heterogeneity: Tau²=0; Chi²=4.54, df=2(P=0.1); I²=55.94%							
Test for overall effect: Z=1.85(P=0.06)							
Test for subgroup differences: Chi²=3.54, df=1 (P=0.06), I²=71.73%							



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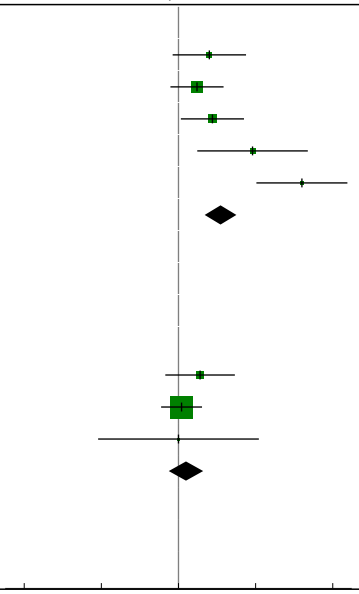
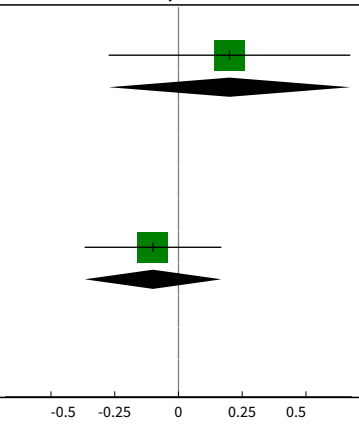
Analysis 2.3. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 3 Head growth (mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.3.1 Sole diet							
Cristofalo 2013	24	8.8 (1.8)	29	7.8 (2.6)		18.69%	1[-0.19,2.19]
Davies 1977	34	7.4 (1.6)	34	6.8 (2)		35.65%	0.6[-0.26,1.46]
Gross 1983	20	8.8 (2.2)	40	7.7 (1.1)		25.27%	1.1[0.08,2.12]
Lucas 1984a	25	11 (3.6)	23	8.6 (2.7)		8.23%	2.4[0.61,4.19]
Tyson 1983	42	12 (2)	34	8 (4)		12.16%	4[2.53,5.47]
Subtotal ***	**145**		**160**			**100%**	**1.36[0.85,1.88]**
Heterogeneity: Tau²=0; Chi²=17.21, df=4(P=0); I²=76.75%							
Test for overall effect: Z=5.2(P<0.0001)							
2.3.2 Supplement							
Lucas 1984b	43	10.1 (2.9)	54	9.4 (2.7)		24.52%	0.7[-0.43,1.83]
O'Connor 2016	162	8.3 (2.9)	164	8.2 (3.2)		70.89%	0.1[-0.56,0.76]
Schanler 2005	88	9 (8)	78	9 (9)		4.59%	0[-2.6,2.6]
Subtotal ***	**293**		**296**			**100%**	**0.24[-0.32,0.8]**
Heterogeneity: Tau²=0; Chi²=0.84, df=2(P=0.66); I²=0%							
Test for overall effect: Z=0.85(P=0.39)							
Test for subgroup differences: Chi²=8.37, df=1 (P=0), I²=88.06%							



Analysis 2.4. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 4 Weight (kg) at 9 months post-term.

Study or subgroup	Favours breast milk N	Favours breast milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.4.1 Sole diet							
Lucas 1984a	48	7.9 (1.3)	62	7.7 (1.2)		100%	0.2[-0.27,0.67]
Subtotal ***	**48**		**62**			**100%**	**0.2[-0.27,0.67]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.83(P=0.41)							
2.4.2 Supplement							
Lucas 1984b	126	7.9 (1.1)	133	8 (1.1)		100%	-0.1[-0.37,0.17]
Subtotal ***	**126**		**133**			**100%**	**-0.1[-0.37,0.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.46)							
Test for subgroup differences: Chi²=1.17, df=1 (P=0.28), I²=14.29%							



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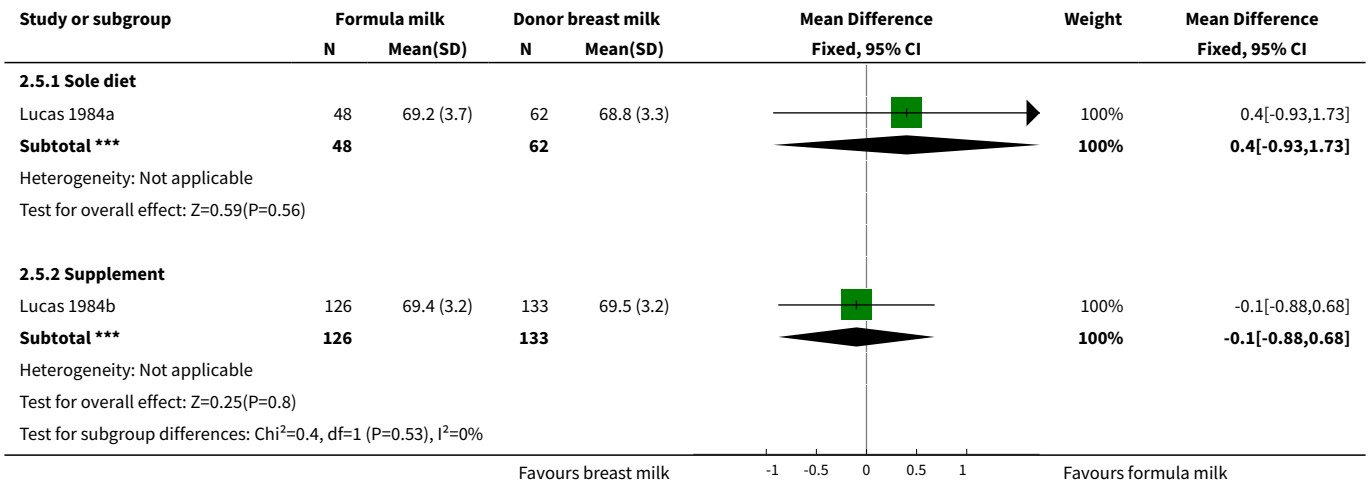
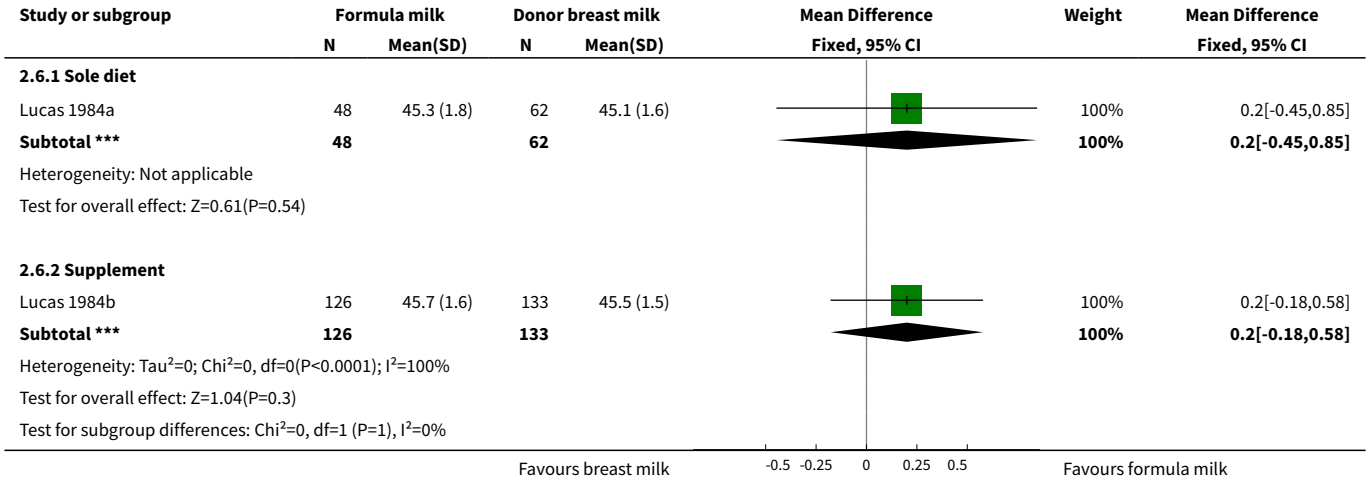
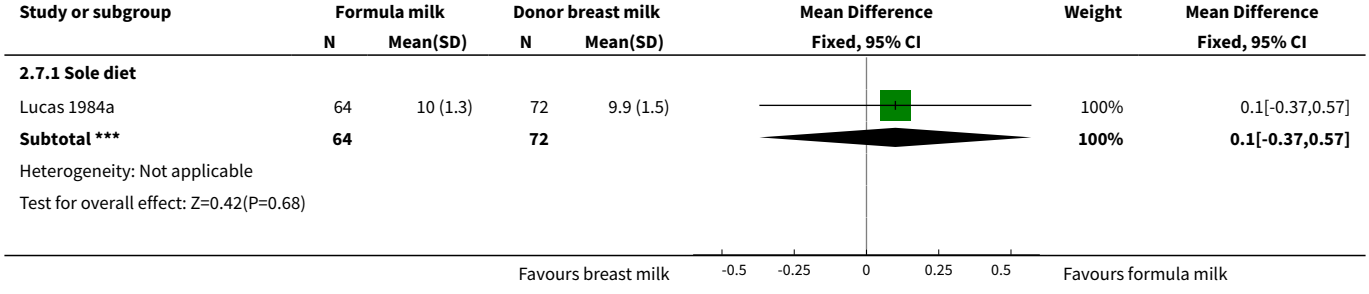
Analysis 2.5. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 5 Length (cm) at 9 months post-term.



Analysis 2.6. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 6 Head circumference (cm) at 9 months post-term.



Analysis 2.7. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 7 Weight (kg) at 18 months post-term.



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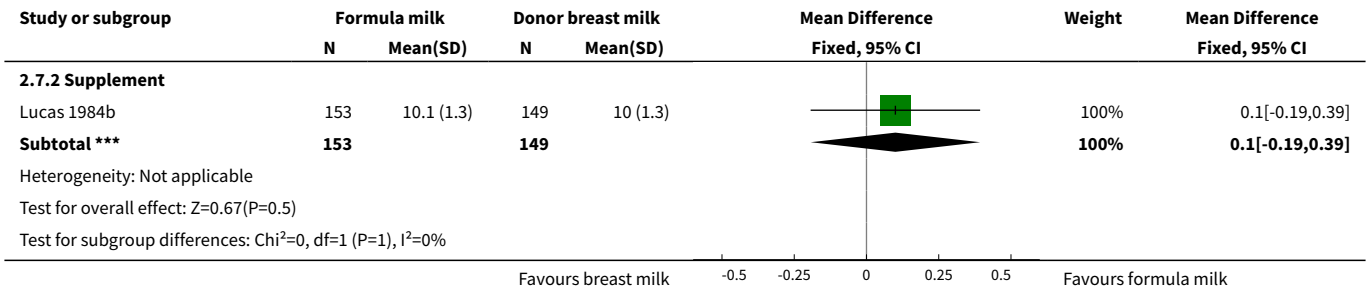
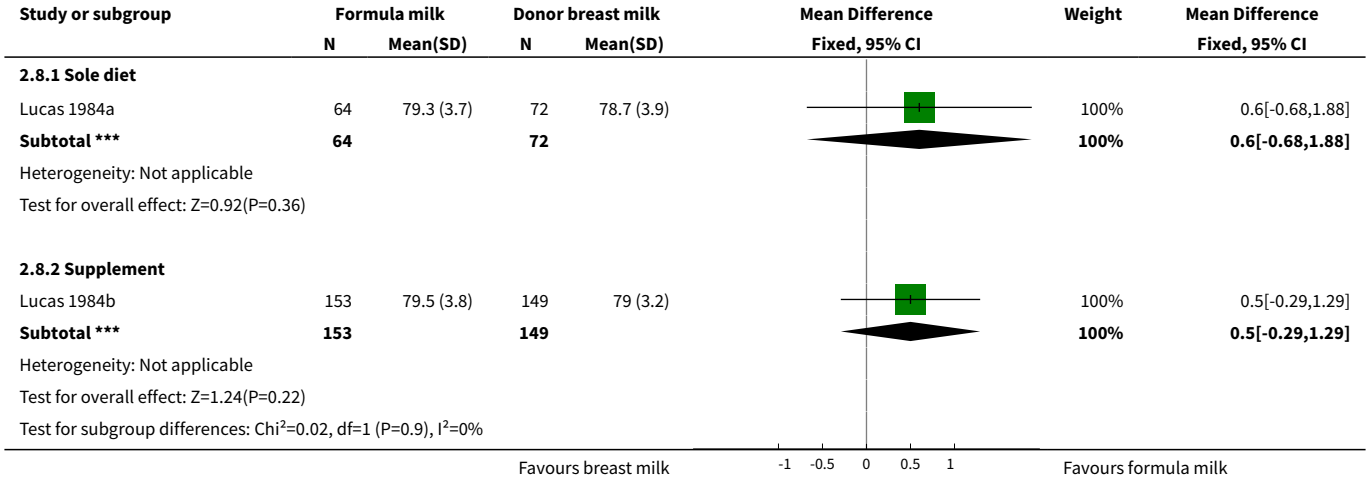
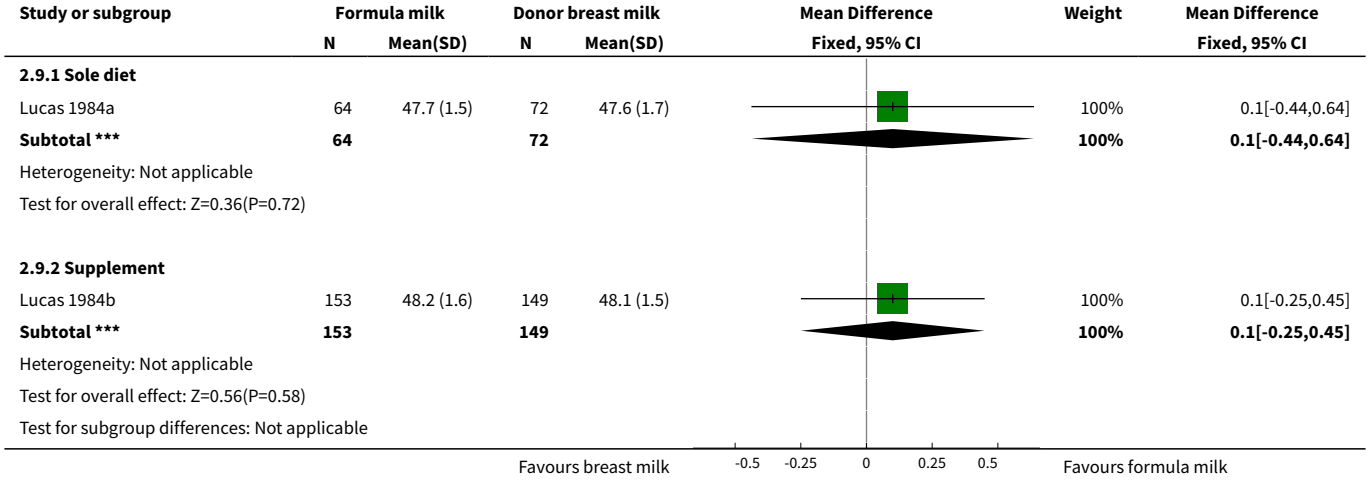


Analysis 2.8. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 8 Length (cm) at 18 months post-term.



Analysis 2.9. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 9 Head circumference (cm) at 18 months post-term.



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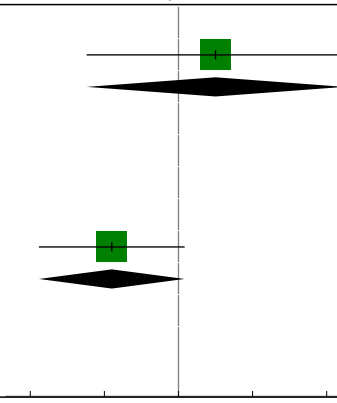
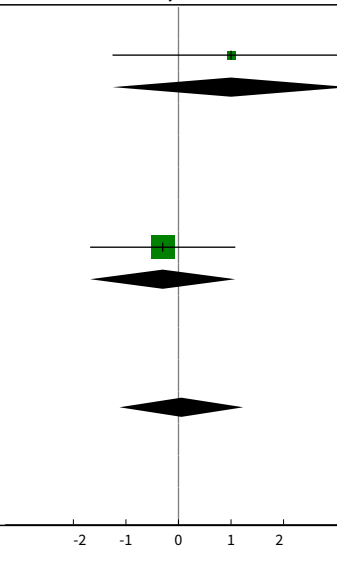
Analysis 2.10. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 10 Weight (kg) at 7.5 to 8 years of age.

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.10.1 Sole diet							
Lucas 1984a	62	22.3 (5.1)	68	21.8 (5)		100%	0.5[-1.24,2.24]
Subtotal ***	**62**		**68**			**100%**	**0.5[-1.24,2.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.56(P=0.57)							
2.10.2 Supplement							
Lucas 1984b	151	22.3 (3.6)	139	23.2 (4.8)		100%	-0.9[-1.88,0.08]
Subtotal ***	**151**		**139**			**100%**	**-0.9[-1.88,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.79(P=0.07)							
Test for subgroup differences: Chi^2=1.89, df=1 (P=0.17), I^2=47%							



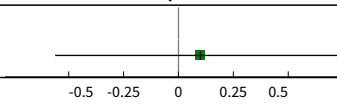
Analysis 2.11. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 11 Length (cm) at 7.5 to 8 years of age.

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.11.1 Sole diet							
Lucas 1984a	62	120.4 (6.6)	68	119.4 (6.5)		27.29%	1[-1.26,3.26]
Subtotal ***	**62**		**68**			**27.29%**	**1[-1.26,3.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.87(P=0.38)							
2.11.2 Supplement							
Lucas 1984b	151	121.3 (6.4)	139	121.6 (5.6)		72.71%	-0.3[-1.68,1.08]
Subtotal ***	**151**		**139**			**72.71%**	**-0.3[-1.68,1.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.43(P=0.67)							
Total ***	**213**		**207**			**100%**	**0.05[-1.12,1.23]**
Heterogeneity: Tau^2=0; Chi^2=0.93, df=1(P=0.34); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							
Test for subgroup differences: Chi^2=0.93, df=1 (P=0.34), I^2=0%							



Analysis 2.12. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 12 Head circumference (cm) at 7.5 to 8 years of age.

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.12.1 Sole diet							
Lucas 1984a	62	51.9 (1.5)	68	51.8 (2.3)		28.15%	0.1[-0.56,0.76]



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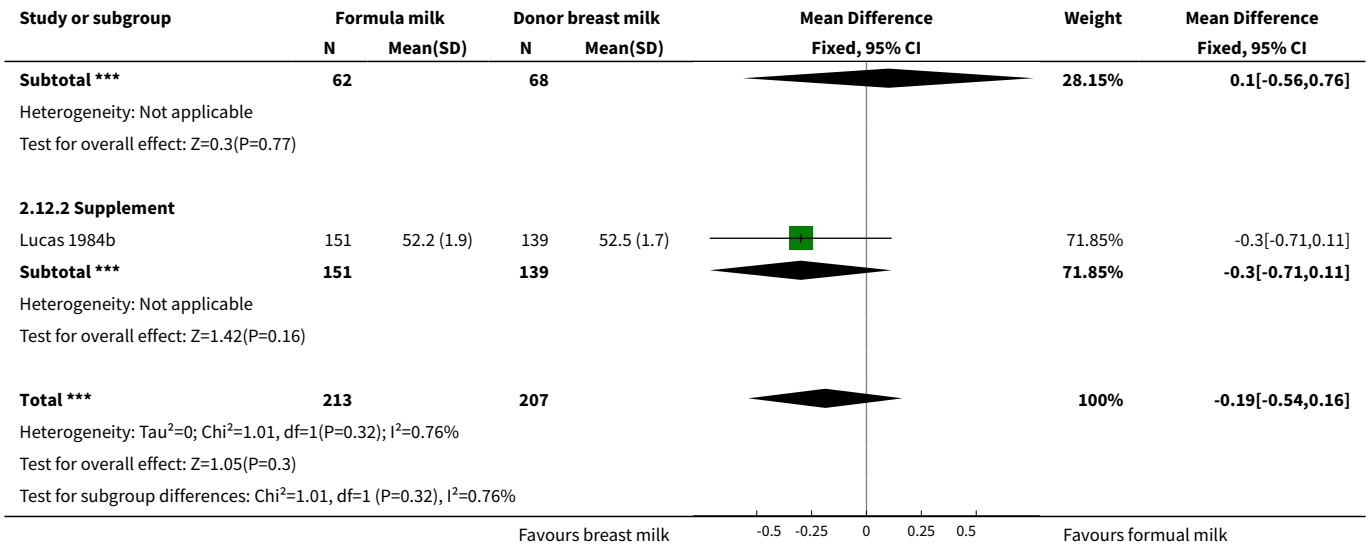
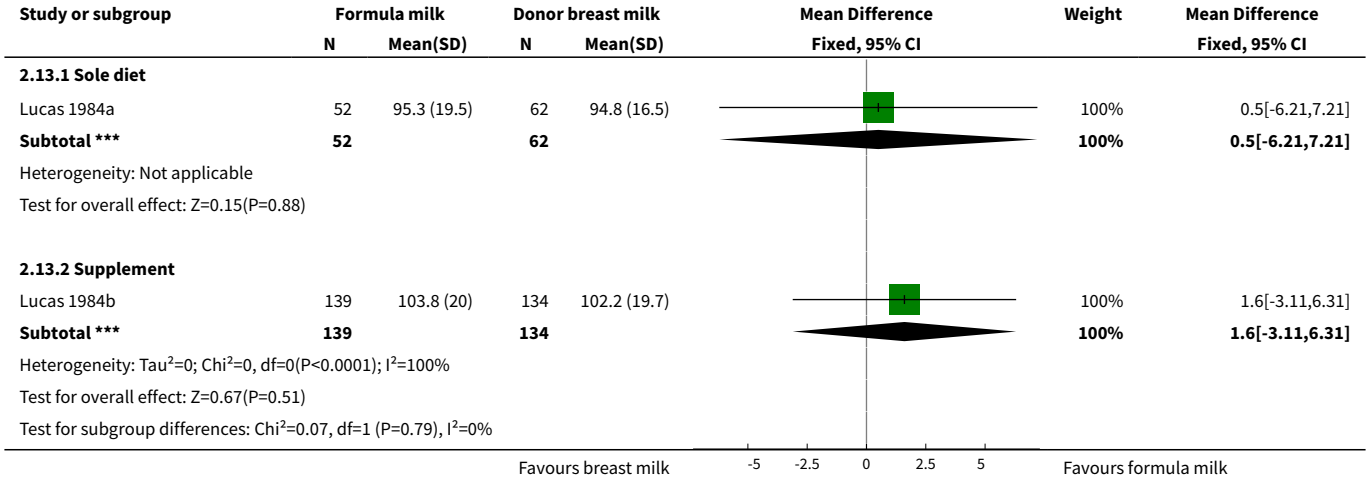
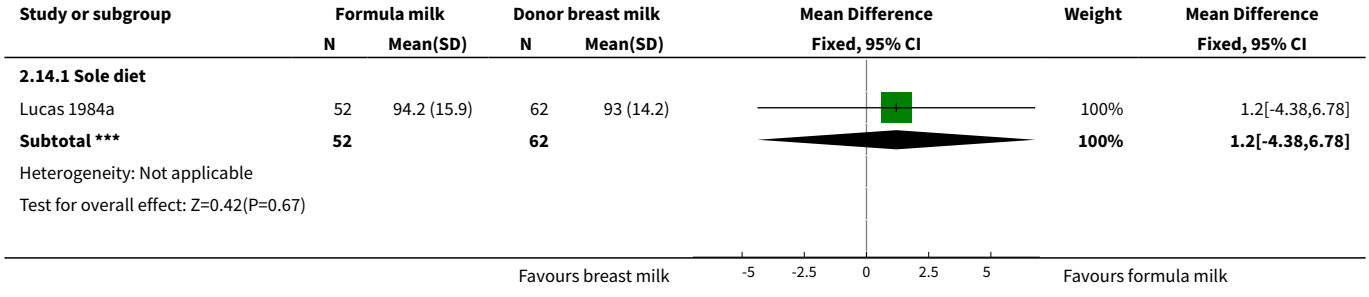


Analysis 2.13. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 13 Bayley Mental Development Index at 18 months.



Analysis 2.14. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 14 Bayley Psychomotor Development Index at 18 months.



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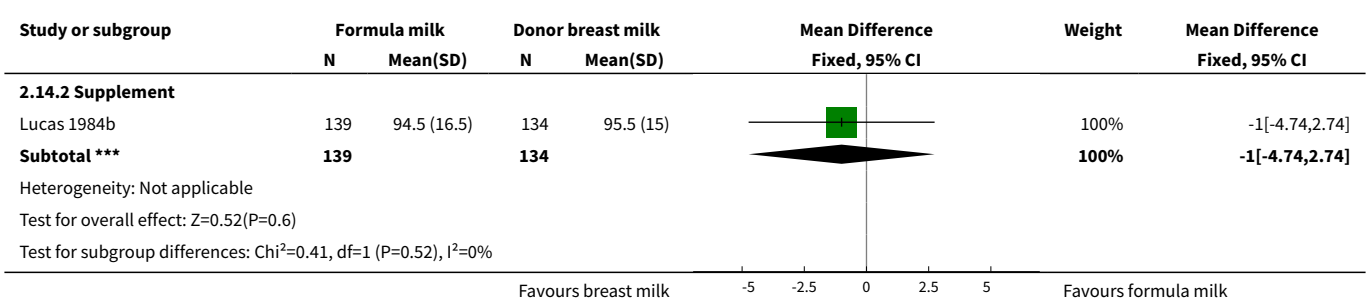
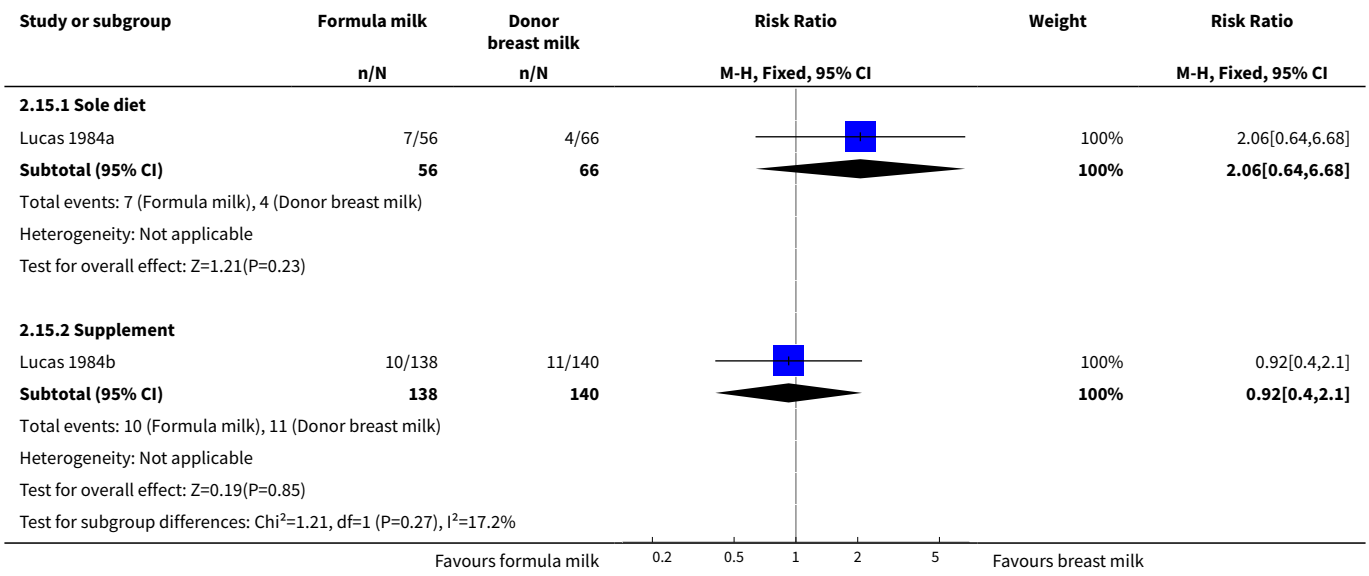
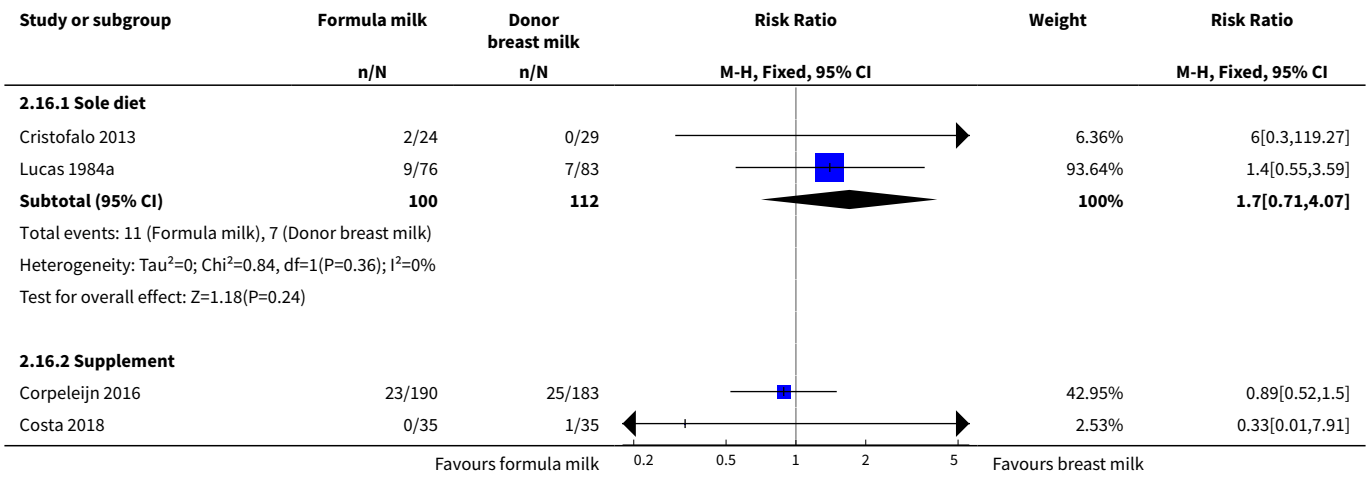


Analysis 2.15. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 15 Neurodevelopmental disability at 18 months.



Analysis 2.16. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 16 All-cause mortality.



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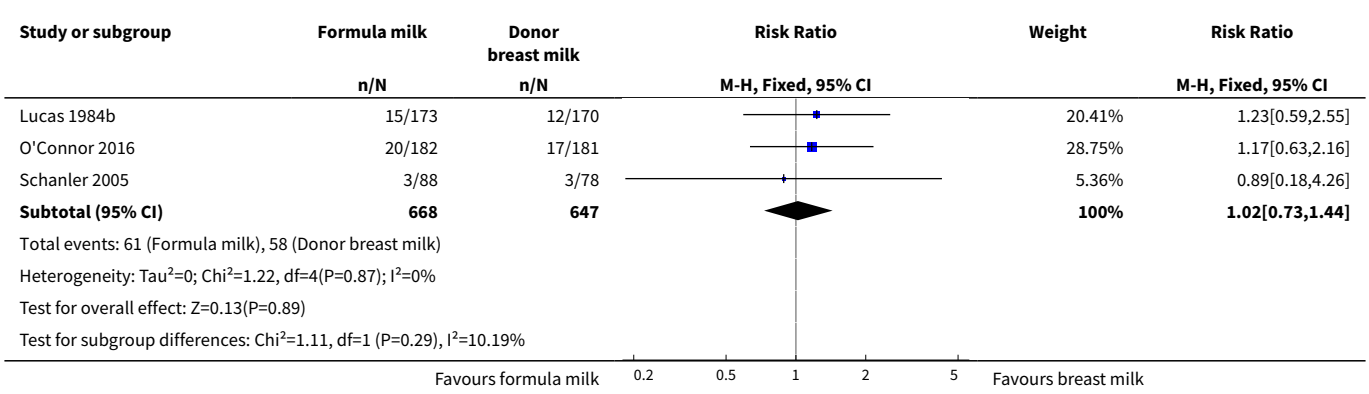
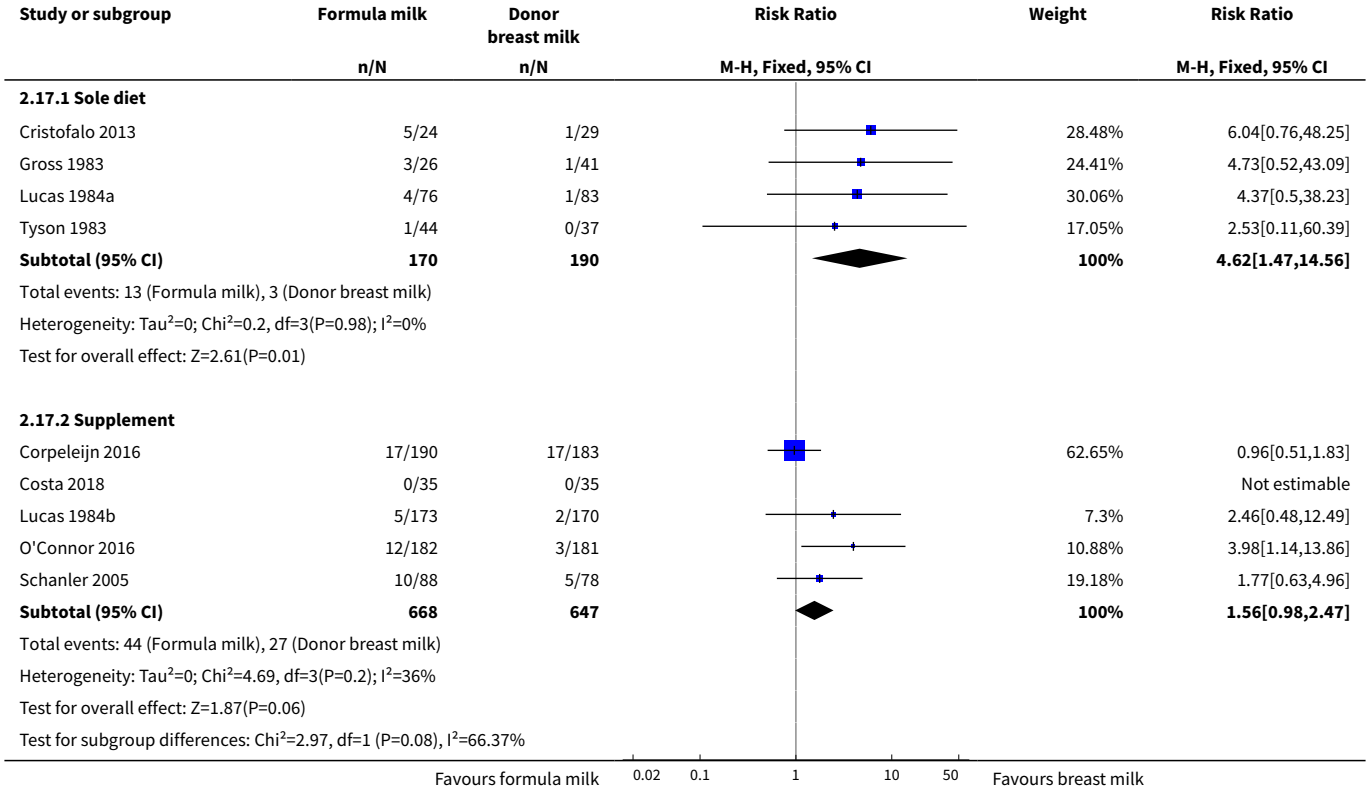
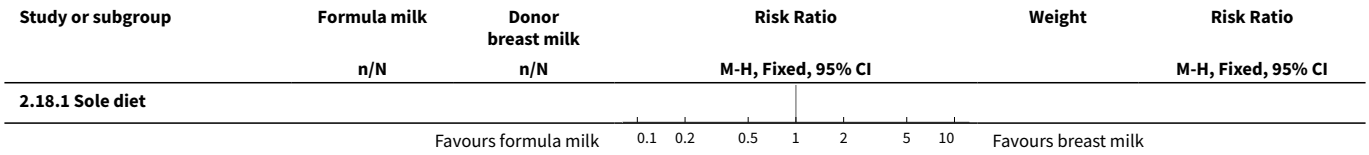


Analysis 2.17. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 17 Necrotising enterocolitis.



Analysis 2.18. Comparison 2 Subgroup analysis: formula versus donated breast milk (DBM) given as (i) sole diet or (ii) a supplement to maternal expressed breast milk, Outcome 18 Incidence of invasive infection.



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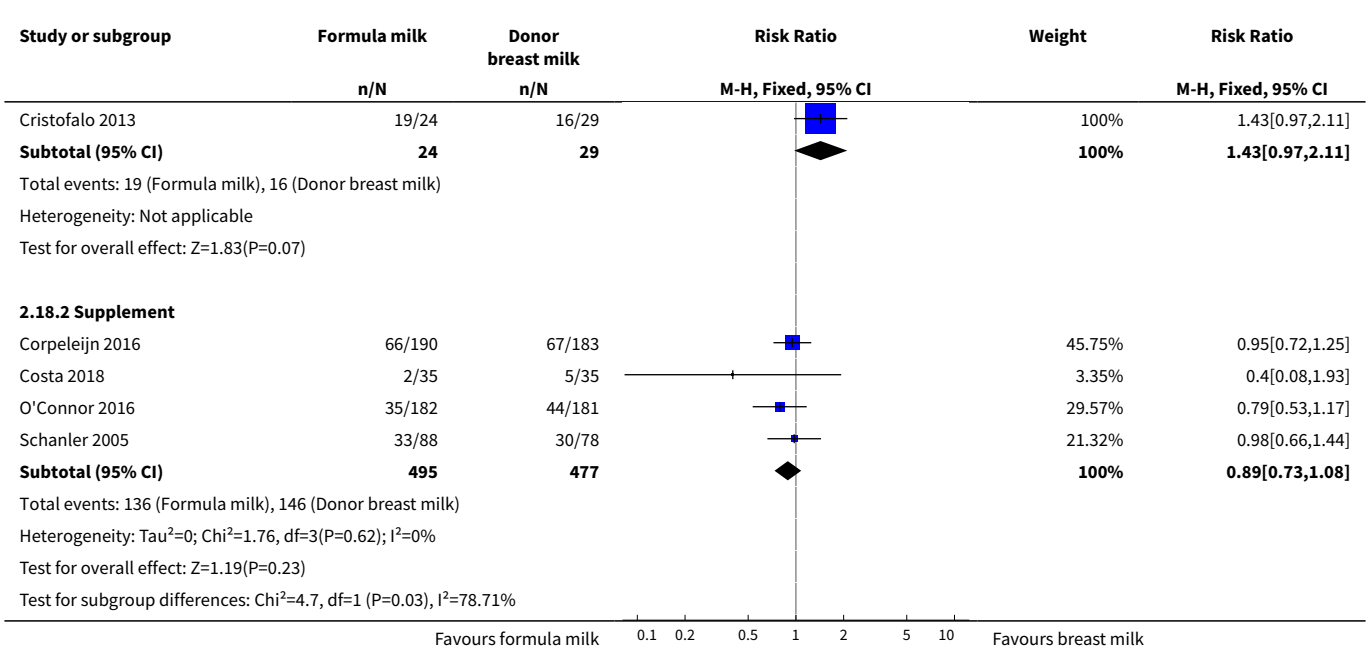

APPENDICES

Appendix 1. Electronic search strategy

CINAHL via EBSCO

Search ID#	**Search Terms**
S1	(MH "Infant, Newborn+")
S2	TX ((neonat* or neo nat*)) OR TX ((newborn* or new born* or newly born*)) OR TX ((preterm or preterms or pre term or pre terms)) OR TX ((preemie$ or premie or premies)) OR TX ((prematur* N3 (birth* or born or deliver*))) OR TX ((low N3 (birthweight* or birth weight*))) OR TX ((lbw or vlbw or elbw)) OR TX infan* OR TX ((baby or babies))
S3	S1 OR S2
S4	(MH "Infant Formula")
S5	TX infant* N2 formula* OR TX pediatric N2 formula* OR TX paediatric N2 formula* OR TX ((baby or babies) N2 formula*) OR TX formula* N2 milk
S6	S4 OR S5
S7	(MH "Milk, Human") OR (MH "Milk Banks")
S8	TX Milk N2 bank* OR TX (milk N2 (donor* or donat*)) OR TX milk N2 shar* OR TX breastmilk N2 bank* OR TX (breastmilk N2 (donor* or donat*)) OR TX breastmilk N2 shar* OR TX (milk N10 (DBM or DHM))
S9	S7 OR S8

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(Continued)

S10	S3 AND S6 AND S9
S11	(MH "Randomized Controlled Trials") OR (MH "Clinical Trials")
S12	(MH "Comparative Studies")
S13	(MH "Evaluation Research")
S14	S11 OR S12 OR S13
S15	S10 AND S14

Cochrane Central Register of Controlled Trials (CENTRAL) via John Wiley's Cochrane Library

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Premature Birth] explode all trees

#3 neonat* or "neo nat*":ti,ab,kw or newborn* or "new born*" or "newly born*":ti,ab,kw or preterm or preterms or "pre term" or "pre terms":ti,ab,kw or preemie* or premie or premies:ti,ab,kw or prematur* near/3 (birth* or born or deliver*):ti,ab,kw (Word variations have been searched)

#4 low near/3 (birthweight* or "birth weight*"):ti,ab,kw or lbw or vlbw or elbw:ti,ab,kw or infan*:ti,ab,kw or baby or babies:ti,ab,kw (Word variations have been searched)

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Infant Formula] explode all trees

#7 infant* near/2 formula*:ti,ab,kw or pediatric near/2 formula*:ti,ab,kw and paediatric near/2 formula*:ti,ab,kw or (baby or babies) near/2 formula*:ti,ab,kw or formula* near/2 milk:ti,ab,kw (Word variations have been searched)

#8 #6 or #7

#9 MeSH descriptor: [Milk, Human] explode all trees

#10 MeSH descriptor: [Milk Banks] explode all trees

#11 Milk near/2 (bank* or donor* or donat* or shar*):ti,ab,kw or Breastmilk near/2 (bank* or donor* or donat* or shar*):ti,ab,kw or milk near/10 (DBM or DHM):ti,ab,kw (Word variations have been searched)

#12 #9 or #10 or #11

#13 #5 and #8 and #12

Embase via OVID

1 Newborn/

2 Prematurity/

3 (neonat$ or neo nat$).ti,ab.

4 (newborn$ or new born$ or newly born$).ti,ab.

5 (preterm or preterms or pre term or pre terms).ti,ab.

6 (preemie$ or premie or premies).ti,ab.

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.

8 (low adj3 (birthweight$ or birth weight$)).ti,ab.

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9 (lbw or vlbw or elbw).ti,ab.

10 infan$.ti,ab.

11 (baby or babies).ti,ab.

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

13 Artifical milk/

14 (infant$ adj2 formula$).ti,ab.

15 (pediatric adj2 formula$).ti,ab.

16 (paediatric adj2 formula$).ti,ab.

17 ((baby or babies) adj2 formula$).ti,ab.

18 (formula$ adj2 milk).ti,ab.

19 13 or 14 or 15 or 16 or 17 or 18

20 Breast milk/

21 Milk Bank/

22 (Milk adj2 bank$).ti,ab.

23 (milk adj2 (donor$ or donat$)).ti,ab.

24 (milk adj2 shar$).ti,ab.

25 (breastmilk adj2 bank$).ti,ab.

26 (breastmilk adj2 (donor$ or donat$)).ti,ab.

27 (breastmilk adj2 shar$).ti,ab.

28 (milk and (DBM or DHM)).ti,ab.

29 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30 12 and 19 and 29

31 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.

32 (cross adj over*).tw.

33 (trial* and (control* or comparative)).tw.

34 ((blind* or mask*) and (single or double or triple or treble)).tw.

35 (treatment adj arm*).tw.

36 (control* adj group*).tw.

37 (phase adj (III or three)).tw.

38 (versus or vs).tw.

39 rct.tw.

40 Crossover Procedure/

41 Double Blind Procedure/

42 Single Blind Procedure/

43 Randomization/

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44 Placebo/

45 exp Clinical Trial/

46 Parallel Design/

47 Latin Square Design/

48 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

49 exp animal/ or exp nonhuman/ or exp animal experiment/ or exp animal model/

50 exp human/

51 49 not 50

52 48 not 51

53 30 and 52

Maternity & Infant Care via OVID

1 (neonat$ or neo nat$).ti,ab.

2 (newborn$ or new born$ or newly born$).ti,ab.

3 (preterm or preterms or pre term or pre terms).ti,ab.

4 (preemie$ or premie or premies).ti,ab.

5 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.

6 (low adj3 (birthweight$ or birth weight$)).ti,ab.

7 (lbw or vlbw or elbw).ti,ab.

8 infan$.ti,ab.

9 (baby or babies).ti,ab.

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

11 (infant$ adj2 formula$).ti,ab.

12 (pediatric adj2 formula$).ti,ab.

13 (paediatric adj2 formula$).ti,ab.

14 ((baby or babies) adj2 formula$).ti,ab.

15 (formula$ adj2 milk).ti,ab.

16 11 or 12 or 13 or 14 or 15

17 Human milk.ti,ab.

18 (Milk adj2 bank$).ti,ab.

19 (milk adj2 (donor$ or donat$)).ti,ab.

20 (milk adj2 shar$).ti,ab. (39)

21 (breastmilk adj2 bank$).ti,ab.

22 (breastmilk adj2 (donor$ or donat$)).ti,ab.

23 (breastmilk adj2 shar$).ti,ab.

24 (milk and (DBM or DHM)).ti,ab.

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25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26 10 and 16 and 25

27 limit 26 to randomised controlled trial

MEDLINE via Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 exp Infant, Newborn/

2 Premature Birth/

3 (neonat$ or neo nat$).ti,ab.

4 (newborn$ or new born$ or newly born$).ti,ab.

5 (preterm or preterms or pre term or pre terms).ti,ab.

6 (preemie$ or premie or premies).ti,ab.

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.

8 (low adj3 (birthweight$ or birth weight$)).ti,ab.

9 (lbw or vlbw or elbw).ti,ab.

10 infan$.ti,ab.

11 (baby or babies).ti,ab.

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

13 Infant Formula/

14 (infant$ adj2 formula$).ti,ab.

15 (pediatric adj2 formula$).ti,ab.

16 (paediatric adj2 formula$).ti,ab.

17 ((baby or babies) adj2 formula$).ti,ab.

18 (formula$ adj2 milk).ti,ab.

19 13 or 14 or 15 or 16 or 17 or 18

20 Milk, Human/

21 Milk Banks/

22 (Milk adj2 bank$).ti,ab.

23 (milk adj2 (donor$ or donat$)).ti,ab.

24 (milk adj2 shar$).ti,ab.

25 (breastmilk adj2 bank$).ti,ab.

26 (breastmilk adj2 (donor$ or donat$)).ti,ab.

27 (breastmilk adj2 shar$).ti,ab.

28 (milk and (DBM or DHM)).ti,ab.

29 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30 12 and 19 and 29

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31 randomized controlled trial.pt.

32 controlled clinical trial.pt.

33 randomized.ab.

34 placebo.ab.

35 drug therapy.fs.

36 randomly.ab.

37 trial.ab.

38 groups.ab.

39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40 exp animals/ not humans.sh.

41 39 not 40

42 30 and 41

Appendix 2. 'Risk of bias' tool

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

For each included study, we 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.

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

For each included study, 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; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

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

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

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

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total

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randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we reincluded missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

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

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

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

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

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

- low risk;
- high risk;
- unclear risk.

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

Appendix 3. GRADE

GRADE considers that evidence from randomised controlled trials is high certainty, but that assessment may be downgraded based on consideration of any of five areas.

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

This results in an assessment of the certainty of a body of evidence in one of four grades.:

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

WHAT'S NEW

Date	Event	Description
7 August 2019	Amended	Declaration of interest updated for Dr. Nicholas D Embleton.

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HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 4, 2001

Date	Event	Description
14 June 2019	New search has been performed	Search updated in May 2019
14 June 2019	New citation required but conclusions have not changed	One additional trial included. Conclusions unchanged
14 February 2018	New search has been performed	Search updated in June 2017 and two new trials included
6 June 2008	Amended	Converted to new review format
18 June 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

William McGuire (WM) and Mary Anthony (MA) developed the protocol and undertook the original review in 2001. Maria Quigley (MQ) and WM revised the protocol and updated the review in 2007 and in 2014. Nicholas D Embleton (NDE), MQ, and WM updated the review in 2018 and 2019.

DECLARATIONS OF INTEREST

MQ: nothing to declare.

NDE declares the following: receiving a research grant award for an RCT of breast milk products by Prolacta Bioscience, 2017; receiving a grant from Danone Early Life Nutrition to support a study on feeding in late and moderately preterm infants, 2018; receiving a grant from Nestle Nutrition for transcriptomic analyses of gut tissue, 2016; lectures with Wyeth Nutrition in 2017, Nestle Nutrition Institute in 2017 and 2018, Philipps in 2017, and Fresenius, 2017.

WM: nothing to declare.

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

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External sources

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

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- Vermont Oxford Network, USA.

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- The Gerber Foundation, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula; *Milk, Human; Infant Nutritional Physiological Phenomena [*physiology]; Infant, Low Birth Weight [*growth & development]; Infant, Premature [*growth & development]; Randomized Controlled Trials as Topic; Weight Gain

MeSH check words

Humans; Infant; Infant, Newborn

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