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Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants (Review)

Quigley M, Embleton ND, Meader N, McGuire W

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[Intervention Review]

Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants

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ABSTRACT

Background

When sufficient maternal milk is not available, donor human milk or formula are the alternative forms of enteral nutrition for very preterm or very low-birthweight (VLBW) infants. Donor human milk may retain the non-nutritive benefits of maternal milk and has been proposed as a strategy to reduce the risk of necrotising enterocolitis (NEC) and associated mortality and morbidity in very preterm or VLBW infants.

Objectives

To assess the effectiveness of donor human milk compared with formula for preventing NEC and associated morbidity and mortality in very preterm or VLBW infants when sufficient maternal milk is not available.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Maternity and Infant Care (MIC) database, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from the earliest records to February 2024. We searched clinical trials registries and examined the reference lists of included studies.

Selection criteria

Randomised or quasi-randomised controlled trials comparing feeding with donor human milk versus formula in very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants.

Data collection and analysis

Two review authors evaluated the risk of bias in the trials, extracted data, and synthesised effect estimates using risk ratio, risk difference, and mean difference, with associated 95% confidence intervals. The primary outcomes were NEC, late-onset invasive infection, and all-cause mortality before hospital discharge. The secondary outcomes were growth parameters and neurodevelopment. We used the GRADE approach to assess the certainty of the evidence for our primary outcomes.

Main results

Twelve trials with a total of 2296 infants fulfilled the inclusion criteria. Most trials were small (average sample size was 191 infants). All trials were performed in neonatal units in Europe or North America. Five trials were conducted more than 40 years ago; the remaining seven trials were conducted in the year 2000 or later. Some trials had methodological weaknesses, including concerns regarding masking of investigators and selective reporting.

Meta-analysis showed that donor human milk reduces the risk of NEC (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.37 to 0.76; I^2 = 4%; risk difference (RD) −0.03, 95% CI −0.05 to −0.01; 11 trials, 2261 infants; high certainty evidence). Donor human milk probably has little or no effect on late-onset invasive infection (RR 1.12, 0.95 to 1.31; I^2 = 27%; RD 0.03, 95% CI −0.01 to −0.07; 7 trials, 1611 infants; moderate certainty evidence) or all-cause mortality (RR 1.00, 95% CI 0.76 to 1.31; I^2 = 0%; RD −0.00, 95% CI −0.02 to 0.02; 9 trials, 2116 infants; moderate certainty evidence).

Authors' conclusions

The evidence shows that donor human milk reduces the risk of NEC by about half in very preterm or VLBW infants. There is probably little or no effect on late-onset invasive infection or all-cause mortality before hospital discharge.

PLAIN LANGUAGE SUMMARY

Does donor human milk prevent severe bowel disorders in very preterm or very low-birthweight infants?

Key messages

• Feeding very preterm or very low-birthweight infants donor human milk rather than formula reduces the risk of necrotising enterocolitis by about half.

• There is probably little or no effect on infection or death rates during the infant's hospital stay.

What is necrotising enterocolitis?

Very preterm infants (those born more than eight weeks early) and very low-birthweight infants (those weighing less than 1.5 kg at birth) are at risk of developing necrotising enterocolitis, a severe condition where tissues in the lining of the infant's bowel become inflamed and die. This condition can lead to serious infection, death, and disability or developmental problems.

What is donor milk?

One way to help prevent necrotising enterocolitis in very preterm or very low-birthweight infants might be to feed them donor human milk (donated by other women) rather than artificial formula (usually adapted from cow milk) when the infant's own mother's milk is not available.

What did we want to find out?

We wanted to know if when a mother's own milk is not available, feeding her very preterm or very low-birthweight infant donor human milk rather than formula reduces the risk of necrotising enterocolitis, serious infection, and death.

What did we do?

We searched for studies and compared and summarised the results of the studies we found. We rated our confidence in the evidence based on factors such as study methods and sizes.

What did we find?

We found 12 trials involving a total of 2296 infants. Feeding very preterm or very low-birthweight infants donor human milk rather than formula reduces the risk of necrotising enterocolitis by about half. There is probably little or no effect on infection or death rates during the infant's hospital stay.

What are the limitations of the evidence?

We are confident in the evidence for an effect on necrotising enterocolitis. We are only moderately confident in the evidence for serious infection and death because there were not enough studies to be certain about the effects, and it is possible that people in the studies knew which treatment they were getting, which could have influenced the results.

How up-to-date is the evidence?

The evidence is current to February 2024.

SUMMARY OF FINDINGS

Summary of findings 1. Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants

Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants

Patient or population: very preterm or very low-birthweight infants
Setting: neonatal unit
Intervention: donor human milk
Comparison: formula

Outcomes	Anticipated absolute effects* (95% CI)		Risk ratio (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with formula	Risk with donor human milk				
Necrotising enterocolitis (before hospital discharge)	71 per 1000	38 per 1000 (26 to 54)	0.53 (0.37 to 0.76)	2261 (11)	⊕⊕⊕⊕ High	Analysis 1.1
Late-onset invasive infection (before hospital discharge)	247 per 1000	277 per 1000 (235 to 324)	1.12 (0.95 to 1.31)	1611 (7)	⊕⊕⊕⊖ Moderate[a]	Analysis 1.2
All-cause mortality (before hospital discharge)	84 per 1000	84 (64 to 110)	1.00 (0.76 to 1.31)	2116 (9)	⊕⊕⊕⊖ Moderate[a]	Analysis 1.3

*__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.

CI: confidence interval

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but 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.

[a]Downgraded one level for imprecision of effect estimate (95% CI around estimate consistent with harm or benefit).

BACKGROUND

Maternal milk is the recommended form of enteral nutrition for very preterm or very low-birthweight (VLBW) infants (Cleminson 2015). When sufficient maternal milk is not available, the available alternatives for feeding very preterm or VLBW infants are donor human milk (donated by other women) and artificial formula (Meek 2022). These may be given as the sole form of enteral feeding or as a supplement to maternal milk (Klingenberg 2012).

Description of the condition

Necrotising enterocolitis (NEC) is a syndrome of acute intestinal necrosis that affects about one in 20 very preterm (born before 32 weeks' gestation) or VLBW (birthweight less than 1500 g) infants (Horbar 2012). Additional risk factors for NEC include being extremely preterm (born before 28 weeks' gestation) or extremely low birthweight (ELBW; birthweight less than 1000 g), and intrauterine growth restriction or compromise (Samuels 2017). Infants who develop NEC experience more episodes of late-onset invasive infection, have lower levels of nutrient intake, grow more slowly, and have longer durations of hospital stay on average than gestation-comparable infants who do not (Battersby 2018; Berrington 2012). The associated mortality rate is about 20%, and there is a high risk of neurodevelopmental problems and disabilities in infants who survive NEC, especially if it is associated with bloodstream infections (Hickey 2018).

Description of the intervention

Intervention

The intervention is donor human milk, that is expressed breast milk from donor mothers. Donor human milk varies with regard to fat, energy, and protein content depending upon the stage of lactation at which it is collected (Colaizy 2021). Concern exists that the macronutrient density (particularly protein) of donor human milk is generally lower than in maternal milk and artificial formula (Gates 2023). The nutrient (particularly fat) content of donor human milk may be reduced by pasteurisation and storage (Peila 2016). Consequently, the nutritional requirements of very preterm or VLBW infants, and especially extremely preterm or ELBW 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 human milk (Hay 1994; Schanler 1995). These deficiencies may have adverse consequences for growth and development. Supplementation of human milk with nutrient fortifiers (typically extracted from cow milk) is an option for increasing nutrient density (Klingenberg 2012). Although this may accelerate short-term growth, uncertainty remains about whether fortification using cow milk extracts increases the risk of enteral feed intolerance or NEC in very preterm or VLBW infants (Brown 2020; Ellis 2019).

Comparison

The comparison to the intervention is artificial formula (usually adapted from cow milk). Formulas vary in energy, protein, and mineral content but can be broadly considered as (Tsang 1993):

- standard 'term' formulas, based on the composition of human milk; the typical energy content is 67 kCal/100 mL to 70 kCal/100 mL;
- nutrient-enriched 'preterm' formulas, energy-enriched (typically up to 80 kCal/100 mL) and variably protein- and mineral-enriched (Fewtrell 1999).

How the intervention might work

In addition to macro- and micronutrients that are optimised by evolution for digestion and absorption by human infants, human milk contains numerous 'immunonutrients' such as secretory immunoglobulin A, lactoferrin, cytokines, enzymes, growth factors, and leucocytes (Walsh 2019). Delivery of these immunological and growth factors to the immature intestinal mucosa may promote postnatal physiological, neuro-endocrinological, and metabolic adaptation in very preterm or VLBW infants (Embleton 2017). Evidence from observational studies suggests that feeding with maternal milk rather than formula is associated with a reduced risk of serious adverse outcomes including NEC and late-onset invasive infection in very preterm and VLBW infants (Cleminson 2015). Although these associations may be confounded by other factors, there have not been any randomised controlled trials of maternal milk versus formula for feeding very preterm or VLBW infants, most likely because of the difficulty of allocating an alternative form of nutrition to an infant whose mother wishes to feed with her own milk (Brown 2019).

Artificial formulas, particularly nutrient-enriched 'preterm' formulas, might provide consistently higher levels of nutrients than donor human milk does. However, formulas do not contain the same immuno-nutritional factors that are present in human milk (Tudehope 2012). Furthermore, although cow milk proteins, carbohydrates, and lipids in formulas are modified to improve digestibility for newborn infants, these are less likely to be tolerated than human milk macronutrients, especially by the immature preterm intestine. Formula feeding might therefore delay the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonisation (Embleton 2017). Intestinal dysmotility and dysbiosis might exacerbate feed intolerance and delay the establishment of enteral feeding independent of parenteral nutrition (Young 2020). Prolonged parenteral nutrition is associated with infectious and metabolic complications that increase mortality and morbidity, prolong hospital stay, and adversely affect growth and development (Walsh 2019).

Why it is important to do this review

Necrotising enterocolitis and its associated complications - particularly late-onset invasive infection - are the most common causes of mortality and serious morbidity beyond the early neonatal period in very preterm or VLBW infants (Berrington 2012). Given the potential for donor human milk to affect these and other important outcomes for very preterm or VLBW 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 to inform practice, policy, and research is merited.

OBJECTIVES

To assess the effectiveness of donor human milk compared with formula for preventing NEC and associated morbidity and mortality in very preterm or VLBW infants when sufficient maternal milk is not available.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) or quasi-RCTs (predictable allocation), including cluster-RCTs. Cross-over studies were not eligible for inclusion because this design would not allow evaluation of the outcomes of interest.

Types of participants

For this 2024 update, we included trials in which participants were very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants, since this population is at high risk of NEC and associated mortality and morbidity. If trials included a broader range of participants, we sought subgroup data for very preterm or VLBW infants from the trial report or the primary investigators. If subgroup data were not available, we included the trial data if most participants were very preterm or VLBW.

Types of interventions

Intervention: enteral feeding with donor human milk (with or without nutrient fortification).

Comparison: enteral feeding with formula (standard term or nutrient-enriched preterm formula).

The allocated milk feed may have been a supplement to maternal milk or have formed the entire enteral intake (sole diet), and should have been the intended enteral diet for at least one week.

All treatment arms of each trial are listed in Characteristics of included studies.

Types of outcome measures

We focused on infant- and family-important outcomes, principally neonatal morbidities that plausibly affect rates of mortality or neurodisability (Jaworski 2022).

Primary outcomes

Severe morbidity and mortality

- NEC before discharge from hospital, confirmed at surgery or autopsy or using standardised clinical and radiological criteria (VON 2021):
  - at least one of: bilious gastric aspirate or emesis; or abdominal distention; or blood in stool; and
  - at least one of: abdominal radiograph showing pneumatosis intestinalis; or gas in the portal venous system; or free air in the abdomen.
- Late-onset invasive infection: positive culture or microscopy of bacteria or fungus from blood or cerebrospinal fluid or from a normally sterile body space (> 48 hours after birth until discharge from hospital).
- All-cause mortality before discharge from hospital.

Secondary outcomes

Growth and development

- In-hospital growth until term equivalent:
  - weight gain (g/kg/day);
  - head circumference growth (mm/week).
- Growth parameters assessed after 12 months' post-term:
  - weight;
  - head circumference;
  - proportion of infants who remained below the 10th percentile for the index population's distribution.
- Neurodevelopmental outcomes assessed after 12 months' post-term:
  - neurodevelopmental scores (e.g. Bayley Mental or Psychomotor Developmental Indices) and classifications of disability, including cerebral palsy and auditory and visual impairment;
  - cognitive and educational outcomes in children aged more than five years old.

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal.

Electronic searches

We searched the following electronic databases using a combination of text words and MeSH terms (see Appendix 1) on 7 February 2024.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2024, Issue 2), in the Cochrane Library
- MEDLINE via Ovid (1946 to February 2024)
- Embase via Ovid (1974 to February 2024)
- Maternity and Infant Care (MIC) database via Ovid (1971 to February 2024)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to February 2024)

We limited the search outputs with filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). We did not apply any language restrictions.

Searching other resources

We searched the following clinical trial registries for ongoing or recently completed trials.

- ClinicalTrials.gov (clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform)

We examined the reference lists of included studies.

We searched for errata or retractions for included studies published on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

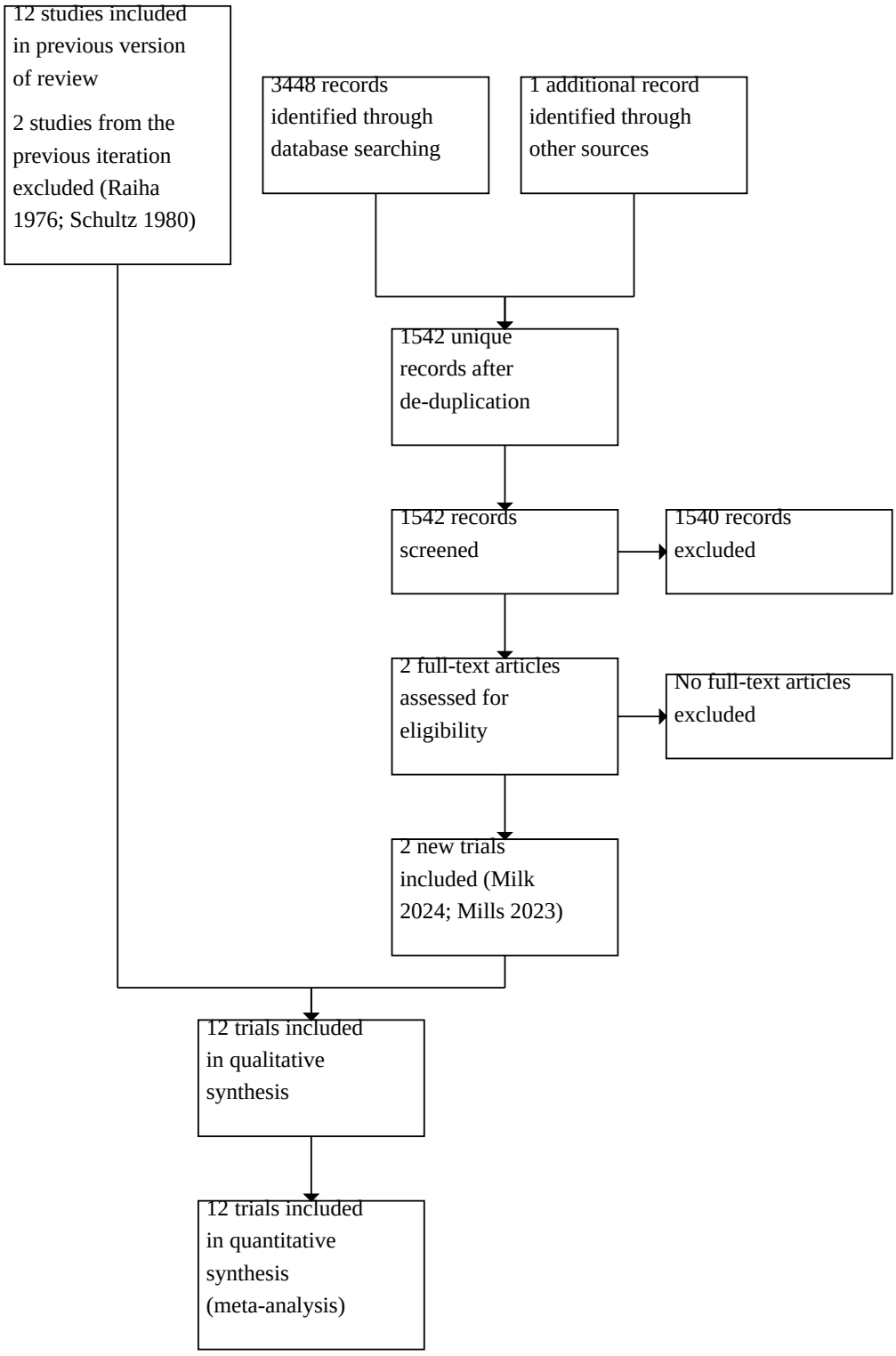
We collected information about the method of randomisation, masking (blinding), intervention, and stratification for each included study. We noted information regarding trial participants (gestational age and birthweight) and clinical outcomes (Types of outcome measures). Where there were multiple publications for a trial, we collated the reports so that each trial, rather than each report, was the unit of interest in the review. Such trials were assigned a single identifier with multiple references.

Selection of studies

We downloaded all titles and abstracts retrieved by the electronic searching to reference management software. We removed duplicates using reference management software and Covidence. Two review authors (NDE, WM) independently screened the titles and abstracts of all studies and assessed the full articles for all trials deemed potentially relevant. We listed any studies excluded at the full-text stage along with the reasons for their exclusion in Characteristics of excluded studies. Any disagreements were discussed until consensus was achieved, with referral to a third review author (MQ) for a final decision as necessary. Information on ongoing studies is provided in Characteristics of ongoing studies.

We described the study selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram: 2024 review update.



Data extraction and management

Two review authors (NDE, WM) independently extracted the following data using a data collection form.

- Study author(s); published or unpublished; year of publication; year in which study was conducted; presence of vested interest by study authors; details of other relevant papers cited.
- Study registration; design; setting, number of centres and location; completeness of follow-up assessment.
- Inclusion criteria and exclusion criteria; participant characteristics (gestational age and birthweight); number randomised; number lost to follow-up or withdrawn; number analysed.
- Intervention initiation, dose, and duration of administration.
- Review outcomes (Types of outcome measures).

Any disagreements were discussed until consensus was reached. 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) in all included trials using the Cochrane RoB 1 tool (Higgins 2011), for the following domains:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- other bias (principally baseline imbalance).

In the case of disagreement, we planned to involve a third review author (MQ). See Appendix 2 for a description of the RoB 1 tool.

For cluster-randomised trials, where groups of individuals rather than individuals were randomised to the different interventions, we planned to assess bias arising from prior knowledge of cluster-allocation (identification/recruitment bias, suggested by baseline imbalances in characteristics of participants rather than of clusters) and bias arising from the timing of identification and recruitment of participants (Higgins 2020).

Measures of treatment effect

For dichotomous data, we presented results using risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CIs). We calculated the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) with 95% CIs if there was a statistically significant reduction (or increase) in RD.

For continuous data, we used the mean difference (MD) when outcomes were measured in the same way between trials. We planned to use the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods. Where trials reported continuous data as median and interquartile range (IQR), and data passed the test of skewness, we planned to convert median to mean and estimate the standard deviation as IQR/1.35.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster-randomised trials. For cluster-randomised trials, 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 2020). We planned to derive the intracluster correlation (ICC) for these adjustments from the trial report or from a similar trial. If an appropriate ICC was unavailable, we would conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.

For trials with multiple arms versus the same control, we combined groups to create a single pair-wise comparison.

Dealing with missing data

We analysed outcome data on an intention-to-treat basis by including all participants in the treatment groups to which they were randomised, regardless of the actual treatment received. We planned to request additional data from trial investigators when data on important outcomes were missing or reported unclearly. If we were unable to obtain the information, we would undertake sensitivity analyses to assess the potential impact on outcomes by excluding those trials with more than 20% missing data. We planned to consider the potential impact of missing data on the findings of the review in the Discussion.

Assessment of heterogeneity

Two review authors (NDE, WM) assessed clinical and methodological variability. A meta-analysis was conducted when both review authors agreed that study participants, interventions, and outcomes were sufficiently similar. To assess heterogeneity in meta-analyses, we inspected forest plots and assessed the direction and magnitude of effects and the degree of overlap between 95% CIs. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected high levels of heterogeneity (I^2 > 75%), we would report the finding and explore possible explanatory factors using prespecified subgroup analyses (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We planned to assess reporting bias by comparing the stated primary and secondary outcomes with the reported outcomes. Where study protocols were available, we compared these to the full publications. We documented trials that evaluated the intervention in a potentially eligible population but did not report any of the primary and secondary outcomes in Characteristics of included studies.

For a meta-analysis with RR data from 10 or more trials, we assessed funnel plot asymmetry visually and with Egger's test (for continuous outcomes; Egger 1997) or Harbord's modification of Egger's test (for dichotomous outcomes; Harbord 2006). If a meta-analysis contained RR data from fewer than 10 trials, we noted our inability to rule out possible publication bias or small-study effects.

Data synthesis

We performed meta-analyses using RevMan software (RevMan 2024).

For categorical outcomes, we calculated the typical estimates of RR and RD, each with its 95% CI. For continuous outcomes, we calculated the MD or the SMD, each with its 95% CI. We used a fixed-effect model to combine data where it was reasonable to assume that the trials estimated the same underlying treatment effect, that is the intervention and the populations and methods of the trials were sufficiently similar. If we judged meta-analysis to be inappropriate, we would analyse and interpret individual trials separately. If there was evidence of clinical heterogeneity, we attempted to explain it based on the different trial characteristics and subgroup analyses.

Subgroup analysis and investigation of heterogeneity

When we detected moderate or high heterogeneity in the RR estimates for the primary outcomes ($I^2 > 75\%$), we would examine the potential causes in subgroup analyses of donor human milk versus formula given as:

- a sole diet; or
- a supplement to maternal milk.

Where sufficient data for subgroup comparison were available, we conducted a stratified meta-analysis and a formal statistical test for interaction to assess effects on heterogeneity (Borenstein 2013). We planned to interpret the test for subgroup differences in effects with caution, given the potential for confounding with other study characteristics and the observational nature of the comparisons.

Sensitivity analysis

We planned to undertake sensitivity analyses for the primary outcomes to test whether key methodological factors may have affected the main result. We assessed how these estimates were affected by including only studies at low risk of bias for all of the following domains:

- selection bias (adequate randomisation and allocation concealment);
- detection or performance bias (adequate masking of intervention and measurement);
- attrition bias (< 20% loss to follow-up for primary outcome assessment); and
- reporting bias (selective reporting).

Given that there is no formal statistical test that can be used for sensitivity analysis, we made informal comparisons between the different ways of estimating the effect under different assumptions. Since statistical significance may be lost with fewer trials included, we did not use changes in the P values to judge whether there was a difference between the main analysis and sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

Two review authors (NDE, WM) used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of the evidence for the following clinically relevant outcomes.

- NEC before discharge from hospital
- Late-onset invasive infection (before hospital discharge)
- All-cause mortality (before hospital discharge)

Two review authors (NDE, WM) used GRADEpro GDT software to create Summary of findings 1, to report the certainty of the evidence for the outcomes listed above (Walsh 2021). We considered evidence from RCTs as high certainty, downgrading by one level for serious (or two levels for very serious) limitations based upon the following domains: design (study limitations), inconsistency across studies, indirectness of the evidence, imprecision of estimates, and presence of publication bias. This approach results in an assessment of the certainty of a body of evidence as one of four grades, as follows.

- 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.

RESULTS

Description of studies

Results of the search

The updated search identified 3448 records through database searching and one additional record from other sources. After removal of duplicates, 1542 records remained. We excluded 1540 irrelevant records and assessed the full texts of two records (see Figure 1). We included both of these two new trials (MILK 2024; Mills 2024).

Included studies

See Characteristics of included studies.

Twelve trials fulfilled the review eligibility criteria (Corpeleijn 2016; Costa 2018; Cristofalo 2013; Davies 1977; Gross 1983; Lucas 1984a; Lucas 1984b; MILK 2024; Mills 2024; O'Connor 2016; Schanler 2005; Tyson 1983).

All trials were undertaken in neonatal units in Europe and North America. Five trials were conducted more than 40 years ago (Davies 1977; Gross 1983; Lucas 1984a; Lucas 1984b; Tyson 1983); the remaining seven trials were conducted in the year 2000 or later (Corpeleijn 2016; Costa 2018; Cristofalo 2013; MILK 2024; Mills 2024; O'Connor 2016; Schanler 2005). Individual infants were allocated randomly to intervention or control groups in all of the trials. No trial used a cluster design.

Participants

The included trials involved a total of 2296 infants (range 28 to 483; average 191). Most participants were clinically stable infants of gestational age at birth < 32 weeks' or birthweight < 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

- Two trials compared feeding with donor human milk versus standard term formula as sole diet (Davies 1977; Gross 1983).
- Ten trials compared feeding with donor human milk versus nutrient-enriched preterm formula, either as the sole diet (Cristofalo 2013; Lucas 1984a; Tyson 1983), or as a supplement to maternal milk (Corpeleijn 2016; Costa 2018; Lucas 1984b; MILK 2024; Mills 2024; O'Connor 2016; Schanler 2005).
- Six trials used donor human milk with multinutrient fortifier added empirically or as indicated (Corpeleijn 2016; Cristofalo 2013; MILK 2024; Mills 2024; O'Connor 2016; Schanler 2005). Cristofalo 2013 used human milk-based fortifier. The other five trials used cow milk-based fortifier.

In general, feeds were allocated 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 their own mother's milk was insufficient (Corpeleijn 2016).

Outcomes

The most commonly reported outcomes were NEC, late-onset invasive infection, mortality until hospital discharge, and growth velocities during the study period. Five trials reported growth or neurodevelopmental outcomes assessed beyond infancy (Gross 1983; Lucas 1984a; Lucas 1984b; MILK 2024; O'Connor 2016).

Excluded studies

We excluded 17 studies following full-text review (Brandstetter 2018; Castellano 2019; Colaizy 2015; Cooper 1984; Hair 2014; Jarvenpaa 1983; Marseglia 2015; Narayanan 1982; O'Connor 2003; Perez 2015; Perrella 2015; Putet 1984; Raiha 1976; Schultz 1980; Sullivan 2010; Svenningsen 1982; Tewari 2018). The most common reasons for exclusion were ineligible study design (nine studies) or intervention (six studies). We excluded two previously eligible trials as they did not assess effects in very preterm or VLBW infants (Raiha 1976; Schultz 1980). See Characteristics of excluded studies.

Ongoing studies

We identified two registered trials (NCT01232725; NCT01390753). These have not yet published or presented data. See Characteristics of ongoing studies.

Risk of bias in included studies

Risk of bias is detailed in Characteristics of included studies and summarised in Figure 2 and Figure 3.

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

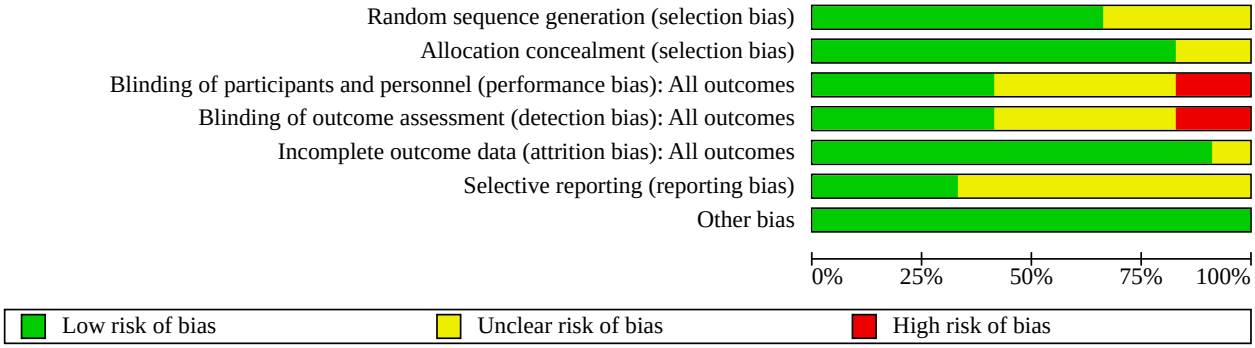
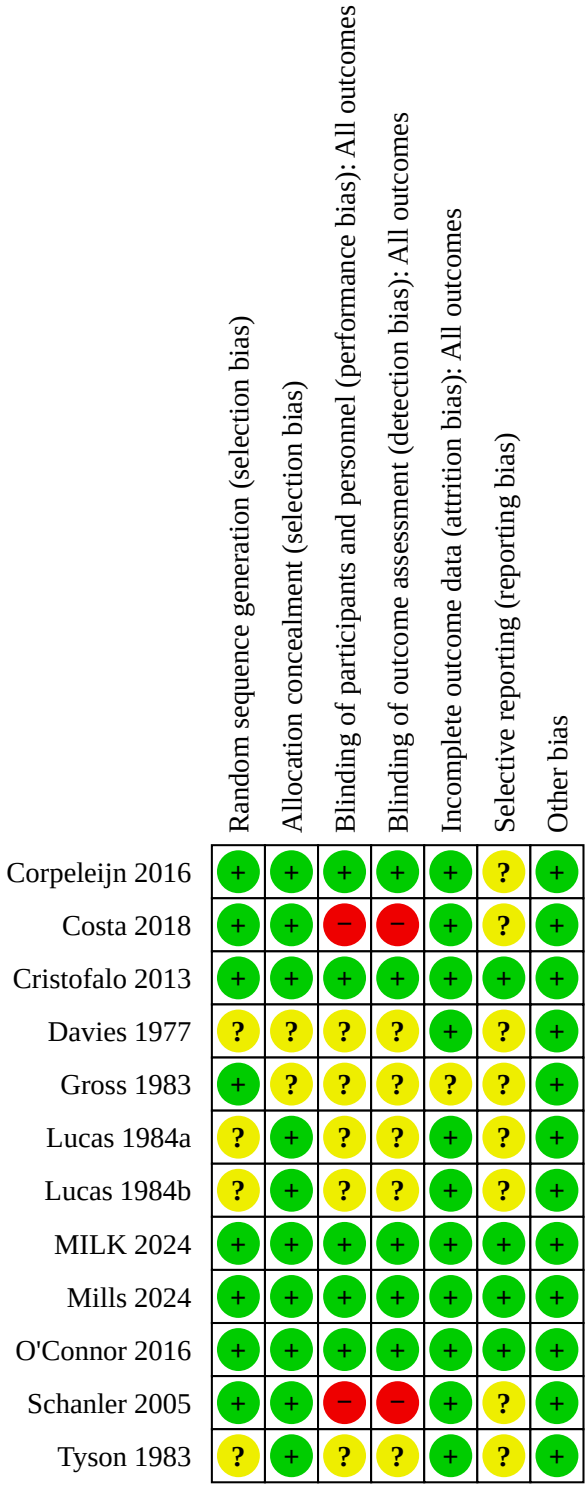


Figure 3. Risk of bias summary.



Allocation

Random sequence generation

Eight trials reported using online randomisation software, computer-generated randomisation, or a computer-driven third-party randomisation service and were assessed as at low risk of bias (Corpeleijn 2016; Costa 2018; Cristofalo 2013; Gross 1983; Mills 2024; O'Connor 2016; Schanler 2005). We judged the other four trials as unclear risk of bias because the selection method was not stated (Davies 1977; Lucas 1984a; Lucas 1984b; Tyson 1983).

Allocation concealment

Ten trials reported adequate allocation concealment methods (sealed, numbered envelopes; central randomisation in blocks) and were assessed as at low risk of bias (Corpeleijn 2016; Costa 2018; Cristofalo 2013; Lucas 1984a; Lucas 1984b; MILK 2024; Mills 2024; O'Connor 2016; Schanler 2005; Tyson 1983). The two other trials did not report methods of allocation concealment and were assessed as at unclear risk of bias (Davies 1977; Gross 1983).

Blinding

Five trials blinded the study and clinical staff or caregivers to the allocated treatments and were assessed as at low risk of bias (Corpeleijn 2016; Cristofalo 2013; MILK 2024; Mills 2024; O'Connor 2016). We judged five trials as having unclear risk of bias because the blinding method was not mentioned (Davies 1977; Gross 1983; Lucas 1984a; Lucas 1984b; Tyson 1983). Two trials did not mask the staff and were unblinded; we assessed these trials as at high risk of bias (Costa 2018; Schanler 2005).

Incomplete outcome data

Eleven trials reported complete follow-up for the in-hospital outcomes' assessment and were assessed as at low risk of attrition bias. In one trial, infants who developed complications (10% of the total enrolled) were withdrawn from the study, therefore the in-hospital growth data for these infants were not presented (Gross 1983).

In those trials that reported data for growth parameters and developmental outcomes assessed beyond infancy (12 months), more than 80% of participants were assessed (low risk of bias) (Gross 1983; Lucas 1984a; Lucas 1984b; O'Connor 2016).

Selective reporting

Corpeleijn 2016 did not report protocol-specified outcome data for short-term growth rate, bone density, Bayley Scores of Infant Development III (at two years of age), and growth rate at two years of age. None of these was a prespecified primary outcome, hence we assessed Corpeleijn 2016 as being at unclear rather than high risk of reporting bias. We assessed another seven trials as at unclear risk of bias, as protocols were not available for assessment (Costa 2018; Davies 1977; Gross 1983; Lucas 1984a; Lucas 1984b; Schanler 2005; Tyson 1983). The other four trials reported no protocol deviations and were therefore assessed as at low risk of bias.

Other potential sources of bias

We did not find evidence of between-group baseline differences in participant characteristics or demographics in the included trials (low risk of bias).

Effects of interventions

See: **Summary of findings 1** Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants

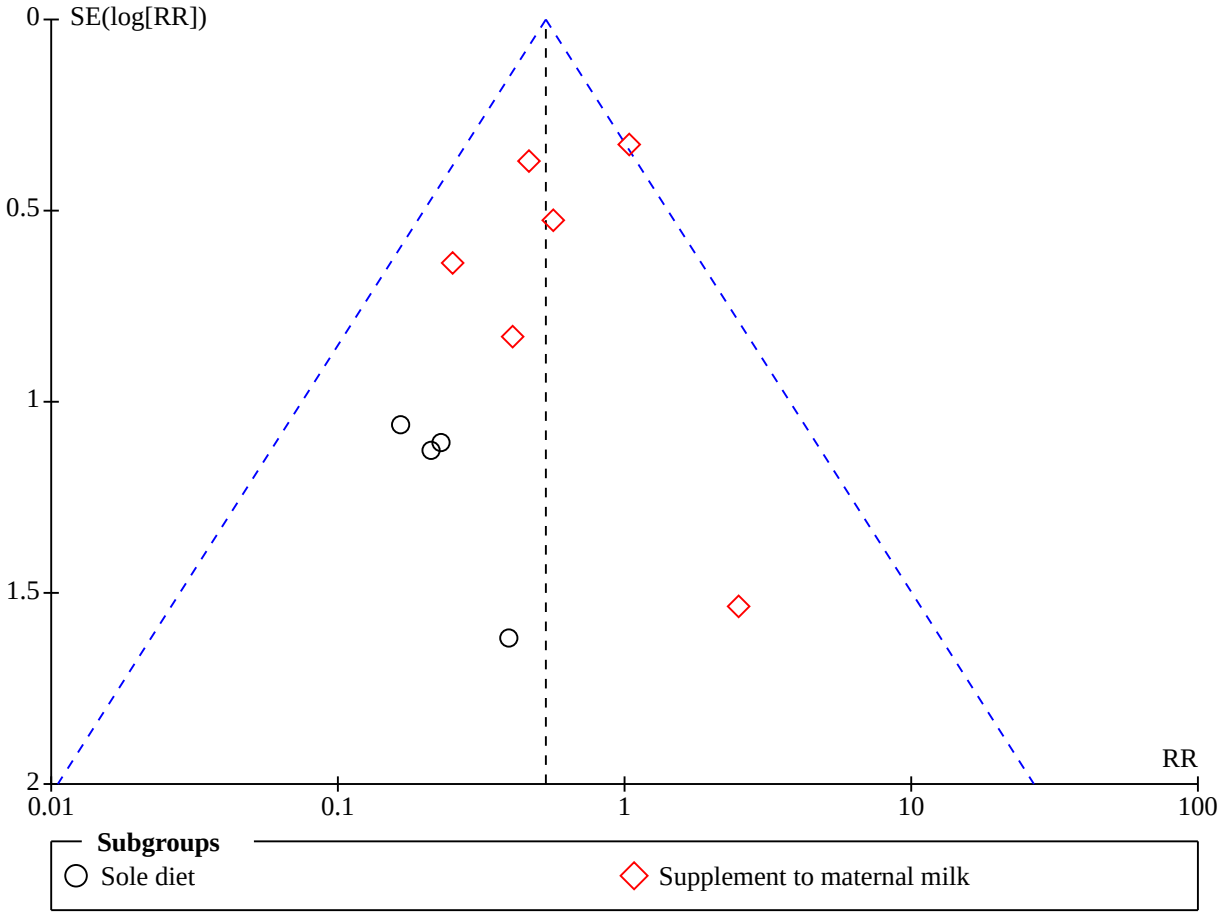
Primary outcomes

Necrotising enterocolitis

Meta-analysis showed that donor human milk reduces the risk of NEC (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.37 to 0.76; I^2 = 4%; risk difference (RD) −0.03, 95% CI −0.05 to −0.01; number needed to treat for an additional beneficial outcome (NNTB) 33, 95% CI 20 to 100; 11 trials, 2261 infants; Analysis 1.1).

Although visual examination suggested some funnel plot asymmetry (Figure 4), the Harbord test was not statistically significant (Bias = −0.82, standard error (SE) = 0.73, P = 0.29).

Figure 4. Funnel plot: donor human milk versus formula - necrotising enterocolitis.



We assessed the certainty of evidence as high using the GRADE approach (Summary of findings 1).

Subgroup analysis for heterogeneity

Not applicable (I^2 = 4%).

Sensitivity analysis for risk of bias

Meta-analysis of data from trials with low risk of bias across all domains showed that donor human milk reduces the risk of NEC (RR 0.39, 95% CI 0.22 to 0.70; I^2 = 0%; RD −0.05, 95% CI −0.08 to −0.02; NNTB 20, 95% CI 12 to 50; 4 trials, 1002 infants) (Cristofalo 2013; MILK 2024; Mills 2024; O'Connor 2016).

Late-onset invasive infection

Meta-analysis showed that donor human milk probably has little or no effect on late-onset invasive infection (RR 1.12, 95% CI 0.95 to 1.31; I^2 = 27%; RD 0.03, 95% CI −0.01 to −0.07; 7 trials, 1611 infants; Analysis 1.2).

There were insufficient RR data points to assess funnel plot asymmetry.

We assessed the certainty of evidence as moderate using the GRADE approach (Summary of findings 1).

Subgroup analysis for heterogeneity

Not applicable (I^2 = 27%).

Sensitivity analysis for risk of bias

Meta-analysis of data from trials with low risk of bias across all domains showed that donor human milk probably has little or no effect on late-onset invasive infection (RR 1.16, 95% CI 0.93 to 1.47; I^2 = 59%; RD 0.03, 95% CI −0.02 to 0.08; 4 trials, 1002 infants) (Cristofalo 2013; MILK 2024; Mills 2024; O'Connor 2016).

All-cause mortality

Meta-analysis showed that donor human milk probably has little or no effect on all-cause mortality (RR 1.00, 95% CI 0.76 to 1.31; I^2 = 0%; RD −0.00, 95% CI −0.02 to 0.02; 9 trials, 2116 infants; Analysis 1.3).

There were insufficient data points to assess funnel plot asymmetry.

We assessed the certainty of evidence as moderate using the GRADE approach (Summary of findings 1).

Subgroup analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for risk of bias

Meta-analysis of data from trials with low risk of bias across all domains showed that donor human milk probably has little or no effect on late-onset invasive infection (RR 1.01, 95% CI 0.68 to 1.52; I^2 = 0%; RD 0.00, 95% CI −0.03 to 0.04; 4 trials, 1002 infants) (Cristofalo 2013; MILK 2024; Mills 2024; O'Connor 2016).

Secondary outcomes

In-hospital growth until term equivalent

Weight change

Meta-analysis showed that donor human milk results in slower weight gain until term equivalent (mean difference (MD) −3.55, 95% CI −4.21 to −2.89 g/kg/day; I^2 = 84%; 9 trials; 1360 infants; Analysis 1.4).

Subgroup analysis for heterogeneity

There was evidence of subgroup differences by sole diet versus supplement, with the effect size larger in the sole diet subgroup (Chi^2 = 28.69, df = 1 (P < 0.001), I^2 = 96.5%).

One trial reported insufficient data to meta-analyse:

- Mills 2024 reported that the change in z-score from birth to hospital discharge was not statistically significantly different between the groups.

Head circumference

Meta-analysis showed that donor human milk results in slower head circumference growth until term equivalent (MD −0.69, 95% CI −1.01 to −0.36 mm/week; I^2 = 69%; 9 trials, 1261 infants; Analysis 1.5).

Subgroup analysis for heterogeneity

There was evidence of subgroup differences by sole diet versus supplement, with the effect size larger in the sole diet subgroup (Chi^2 = 12.41, df = 1 (P < 0.001), I^2 = 91.9%).

Two trials reported insufficient data to meta-analyse:

- Costa 2018 did not detect a between-group difference at 36 weeks' postmenstrual age;
- Mills 2024 reported that the change in z-score from birth to term equivalent was not statistically significantly different between groups.

Growth parameters assessed after 12 months' post-term

Two trials reported growth parameters assessed at 18 months' post-term (Lucas 1984a; Lucas 1984b). Meta-analysis showed that donor human milk has little or no effect on weight (MD −0.10, 95% CI −0.35 to 0.15 kg; I^2 = 0%; 2 trials, 438 infants; Analysis 1.6) or head circumference (MD −0.10, 95% CI −0.39 to 0.19 cm; I^2 = 0%; 2 trials, 438 infants; Analysis 1.7).

Proportion of infants who remained below the 10th percentile for the index population's distribution

No trial reported this outcome.

Neurodevelopmental outcomes assessed after 12 months' post-term

Five trials reported neurodevelopmental outcomes measured using validated assessment tools in children aged at least 12 months' post-term (Gross 1983; Lucas 1984a; Lucas 1984b; MILK 2024; O'Connor 2016).

Developmental indices

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

Meta-analysis of data from Lucas 1984a and Lucas 1984b showed that donor human milk has little or no effect on Bayley Mental Development Indices (MD −1.24, 95% CI −5.09 to 2.62; I^2 = 0%; 387 infants; Analysis 1.8) and Psychomotor Development Indices (MD 0.32, 95% CI −2.79 to 3.43; I^2 = 0%; Analysis 1.9) at 18 months' post-term.

Meta-analyses of data from MILK 2024 and O'Connor 2016 showed that donor human milk has little or no effect on Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) assessments at 18 to 22 months' corrected age (Analysis 1.10):

- Cognitive: MD −0.84, 95% CI −3.43 to 1.76 (I^2 = 0%);
- Language: MD −0.53, 95% CI −3.50 to 2.43 (I^2 = 30%);
- Motor: MD −0.92, 95% CI −3.84 to 2.00 (I^2 = 0%).

Cerebral palsy

Meta-analysis of data from four trials (1124 infants) showed that donor human milk has little or no effect on cerebral palsy (RR 0.99, 95% CI 0.66 to 1.46; I^2 = 42%; Analysis 1.11).

Hearing impairment

Analysis of data from O'Connor 2016 showed that donor human milk has little or no effect on hearing impairment (RR 0.98, 95% CI 0.29 to 3.32; Analysis 1.12).

Visual impairment

Analysis of data from O'Connor 2016 showed that donor human milk has little or no effect on visual impairment (RR not estimable - no events; RD 0.00, 95% CI −0.01 to 0.01; Analysis 1.13).

Severe neurodevelopmental disability

Meta-analysis of data from MILK 2024 and O'Connor 2016 (782 infants) showed that donor human milk has little or no effect on the proportion of children with Bayley-III scores < 70 at 18 to 22 months' corrected age (Analysis 1.14):

- Cognitive: RR 1.06, 95% CI 0.78 to 1.45 (I^2 = 0%);
- Language: RR 1.00, 95% CI 0.78 to 1.28 (I^2 = 24%);
- Motor: RR 0.96, 95% CI 0.71 to 1.29 (I^2 = 30%).

Meta-analysis of data from Lucas 1984a and Lucas 1984b (400 infants) showed that donor human milk has little or no effect on severe neurodevelopmental disability as assessed by the Amiel-Tison 1986 classification (RR 0.83, 95% CI 0.43 to 1.60; I^2 = 17%; Analysis 1.15) at 18 months' post-term.

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

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

DISCUSSION

Summary of main results

We included 12 RCTs in which a total of 2296 very preterm or VLBW infants participated. Meta-analysis shows that feeding with donor human milk compared with formula reduces the risk of NEC by about half. The available data show that donor human milk probably results in little or no difference in the risk of late-onset invasive infection or all-cause mortality prior to hospital discharge.

Overall completeness and applicability of evidence

These data are likely to be relevant to current practice, as most of the trials (in particular those with low risk of bias) were conducted since the year 2000. These trials employed broad eligibility criteria to recruit very preterm or VLBW infants including those thought to be at high risk of developing NEC due to intrauterine growth restriction and abnormal foetal circulatory distribution or flow. This enhances the applicability of the findings, since this is the population for which most clinical uncertainty and variation in practice with regard to enteral feeding strategies exists (Klingenberg 2012).

However, all the data in this review were from trials undertaken in neonatal care centres in high-income countries. It is less clear how applicable this evidence is to neonatal care practices in resource-limited settings in low- or middle-income countries where severe infection is an important cause of mortality and morbidity. Although the nutritional and immunological advantages of early feeding with human milk might remain, it is necessary to consider context-specific issues such as capacity for safe donor human milk collection, screening, storage and handling (Taylor 2018). Cost-effectiveness of donor human milk for very preterm or VLBW infants may vary by setting and resource availability. Whether the financial and opportunity costs of maintaining a donor human milk service may be better allocated to other interventions (e.g. lactation support) needs to be considered (Zanganeh 2021).

The amount of donor human milk or formula that infants received varied because it was dependent on the mother's own milk supply. For example, infants participating in Corpeleijn 2016 received donor human milk only during the first 10 days after birth, acting as a "bridge" to receipt of maternal milk. Comparable recent trials allocated infants to receive donor human milk (or formula) for up to between 90 and 120 days after birth if an infant's maternal milk supply remained insufficient (MILK 2024; O'Connor 2016). Understanding how these different approaches affect outcomes is important when considering whether or how to integrate donor human milk provision within lactation support programmes that aim to enhance and prioritise maternal milk availability and use (Shenker 2023).

Quality of the evidence

Meta-analysis shows that one fewer case of NEC will occur in every 33 infants who receive donor human milk rather than formula as the sole diet or as a supplement to maternal milk. A sensitivity analysis of those trials at low risk of bias across all domains showed a similar effect, with one fewer case of NEC for every 20 infants who receive donor human milk rather than formula.

This evidence is of high certainty. Although there was concern about some funnel plot asymmetry (Figure 4), the Harbord test suggested that small-study bias is unlikely to have inflated the effect size estimate. This is reassuring, since small-study bias (including publication bias; the tendency for articles that report large or statistically significant effects to be submitted and accepted for publication (Gale 2020)) has become evident as an important contributor to exaggerated effect size estimates in other meta-analyses of nutritional interventions to improve outcomes in very preterm or VLBW infants (Pammi 2020; Sharif 2023).

We downgraded the certainty of evidence to moderate for late-onset invasive infection and all-cause mortality before hospital discharge due to the existence of imprecision in the estimate of effect, with each meta-analysis generating 95% CIs that included benefit as well as small or no benefit or harm. Although the total number of participants in the 12 included trials was more than 2200, not all trials contributed data to these meta-analyses, and estimates of effect were consequently imprecise. The point estimate for all-cause mortality was null (RD −0.00, 95% CI −0.02 to 0.02), but the bounds of the 95% CI are consistent with an NNTB of 50 infants and a number needed to treat for an additional harmful outcome (NNTH) of 50 infants. A further limitation is that these meta-analyses contained insufficient data points (at least 10) to make funnel plot inspection and regression analysis valid and reliable (Higgins 2020).

Heterogeneity was not a concern in the meta-analyses of the primary outcomes. For the secondary outcomes, however, moderate or high heterogeneity was evident in the meta-analyses of hospital growth parameters (Analysis 1.4; Analysis 1.5). Consequently, the finding that feeding with donor human milk (particularly as sole diet) is associated with slower rates of weight gain and head growth during birth hospitalisation should be interpreted with caution. Five of the trials that contributed data to these meta-analyses were undertaken more than 40 years ago. These trials varied with respect to the type of donor human milk (typically unfortified) and type of formula. Four of these trials assessed donor human milk as the sole diet. In contrast, the trials undertaken in the past 25 years compared feeding with donor human milk with added multinutrient fortifier versus preterm formula, typically as a supplement to maternal milk. These findings are more likely to be applicable to current practice in high-income countries where multinutrient fortification of human milk is commonly undertaken (Klingenberg 2012).

Several 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

For the 2024 update of this review, we revised the inclusion criteria to reflect contemporary clinical context and practice (see: Differences between protocol and review). We redefined the primary outcomes as NEC, late-onset infection, and all-cause mortality before hospital discharge (previously growth parameters and development). Preventing NEC and associated complications (rather than increasing growth rates) is now the main reason for giving donor human milk to very preterm and VLBW infants (Walsh 2021). We restricted the population of interest to very preterm or VLBW infants (previously all preterm or low-birthweight infants) in order to focus on and enhance applicability to those infants at high risk of developing NEC and associated complications. We adopted a pragmatic approach and continued to include older trials that recruited some preterm or low-birthweight infants providing most participants were very preterm or VLBW infants (Gross 1983; Lucas 1984a; Lucas 1984b). Those trials were conducted in the 1980s before care practices that reduced the risk of NEC across the preterm and low-birthweight population, notably antenatal corticosteroid therapy, were widely adopted. However, these changes may have introduced selection bias, since we were aware of potential impacts on the excluded trials or subgroup data.

Another concern with the review process is the possibility that the finding of the effect on NEC is 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 were 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.

Agreements and disagreements with other studies or reviews

Our findings are broadly consistent with another recent systematic review of trials of donor human milk versus formula for very preterm or VLBW infants (Altobelli 2020). This analysis has not yet been updated to include data from two recent trials (MILK 2024; Mills 2024).

The implications for practice and research of our findings are reflected in guidelines and policy documents, including those published by the American Academy of Pediatrics (Abrams 2017; Meek 2022) and the World Health Organization (WHO 2023).

AUTHORS' CONCLUSIONS

Implications for practice

Feeding with donor human milk compared with formula reduces the risk of NEC by about half in very preterm or very low-birthweight (VLBW) infants. The available evidence shows that donor human milk probably has little or no effect on late-onset invasive infection or all-cause mortality. Donor human milk is associated with slower growth in hospital, but there was little or no effect on growth or neurodevelopment beyond infancy.

Implications for research

In high-income countries, further trials of feeding very preterm or VLBW infants with donor human milk versus formula (when there is insufficient maternal milk) are now unlikely to be considered a research priority. Trials may still be merited in some resource-limited settings in low- or middle-income countries. Further research efforts to assess acceptability and cost-effectiveness may help inform context- or setting-specific practice and policy (Buckle 2017; Taylor 2018).

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Mohan Pammi MD, PhD, MRCPCH, Baylor College of Medicine, Houston, USA;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Addie-Ann Smyth, Cochrane Central Editorial Service;
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- Peer reviewers (provided comments and recommended an editorial decision): Dr Natalie Shenker, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, W12 0NN (clinical/content review); Jessica D'Urbano, University of Udine, Italy (consumer review); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); Zosia Beckles, University of Bristol (search review).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Corpeleijn 2016

Study characteristics	
Methods	Randomised controlled trial
Participants	373 VLBW infants with insufficient maternal breast milk during the first 10 days after birth 6 neonatal units in the Netherlands, 2012 to 2014
Interventions	Donor human milk (N = 183) versus preterm formula (N = 190) given as a supplement to maternal milk (with cow's milk-based multinutrient fortifier) Intervention was given during **first 10 days after birth** only.
Outcomes	• NEC • Invasive infection • Mortality during the first 60 days after birth
Notes	**Funding source**: Mead Johnson Nutrition **Trial registration:** trialregister.nl Identifier NTR3225

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	(Quote:) "Online randomisation software"
Allocation concealment (selection bias)	Low risk	Computer randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Families and clinicians (quote:) "blinded"

Corpeleijn 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	99% assessment for primary outcome
Selective reporting (reporting bias)	Unclear risk	Protocol specified growth rate, bone density, Bayley Scores of Infant Development III (at 2 years of age), and growth parameters at 2 years of age as outcomes to be assessed - these are not reported.
Other bias	Low risk	No evidence imbalance in baseline demographics

Costa 2018

Study characteristics	
Methods	Randomised controlled trial
Participants	70 infants (< 33 weeks') with insufficient maternal breast milk during the first 14 days after birth. 1 neonatal unit in Italy, 2015
Interventions	Donor human milk (N = 35) versus preterm formula (N = 35) given as a supplement to maternal milk (nutrient fortification policy not described)
Outcomes	• Time to full enteral feeding (150 mL/kg/day) • Invasive infection • NEC • BPD • Mortality until 36 weeks' PMA
Notes	Fortification policy not described or available from investigator. **Funding source**: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	(Quote:)"Computer-generated list of random numbers"
Allocation concealment (selection bias)	Low risk	(Quote:)"sequence was concealed from researchers"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Families and clinicians not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors not masked

Costa 2018 *(Continued)*

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	Low risk	No evidence imbalance in baseline demographics

Cristofalo 2013

Study characteristics	
Methods	Randomised controlled trial
Participants	53 newborn infants: birthweight 500 g to 1250 g. 7 neonatal intensive care units: 6 in the USA, 1 in Austria, 2010 to 2012
Interventions	Fortified donor human milk (N = 29) versus preterm formula (N = 24). Assigned until 91 days after birth, or discharge, or oral feeding at least 50% of feeds
Outcomes	• Duration of parenteral nutrition • Growth rates (weight, head circumference) • Respiratory support • NEC
Notes	Additional information on methods courtesy of Dr Cristafalo (April 2014) **Funding source**: Prolacta Bioscience

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 of participants and personnel (performance bias) All outcomes	Low risk	Investigators, caregivers, and families were masked
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up

Cristofalo 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	No deviations from protocol
Other bias	Low risk	No evidence imbalance in baseline demographics

Davies 1977

Study characteristics	
Methods	Randomised controlled trial
Participants	28 preterm infants of 28 to 32 weeks' gestation. Department of Child Health, University Hospital of Wales, Cardiff, 1972 to 1973
Interventions	Unfortified donor human milk (N = 14) versus term formula milk (N = 14). Assigned from birth for 2 months
Outcomes	• Weight gain • Increase in head circumference and length from birth until 2 months
Notes	Infants of mothers who wished to breastfeed were initially given expressed breast milk if unable to feed naturally. There were 2 such infants; their feeding group was not specified, and the results for these infants were not presented separately. Given that this applies to only 2 out of 68 infants, we have included this study in the review. **Funding source**: not declared

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 of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (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	Low risk	No evidence imbalance in baseline demographics

Gross 1983

Study characteristics	
Methods	Randomised controlled trial
Participants	67 preterm infants (27 to 33 weeks) with birthweight < 1600 g. Department of Pediatrics, Duke University, USA, 1980 to 1982
Interventions	Unfortified, pasteurised donor human milk (N = 41) versus term formula (N = 26) assigned until the infant reached a weight of 1800 g or until withdrawn from the study because of feeding intolerance or NEC
Outcomes	• Weight, length, and head circumference, from regaining birthweight until reaching 1800 g • Data on adverse events can be determined, although these were not primary endpoints of the study.
Notes	Although the report provided information on adverse outcomes, the 7 affected infants were withdrawn from the study and not included in the analyses of growth rates; growth data are reported for 20 infants in each trial arm. **Funding source**: Mead Johnson Nutrition

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 (Quote:) "Any infant withdrawn from the study was replaced by the next one enrolled"; implies lack of allocation concealment for these infants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (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. 100% follow-up and low risk of bias for mortality and NEC.
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	No evidence of imbalance in baseline demographics

Lucas 1984a

Study characteristics	

Lucas 1984a *(Continued)*

Methods	Randomised controlled trial
Participants	159 infants of birthweight < 1850 g.* Early 1980s in 5 neonatal units in the Anglia region of the UK
Interventions	Donor (mainly "drip") human milk (N = 83) versus preterm formula (N = 76) assigned until the infant reached a weight of 2000 g or until discharge from the neonatal unit. Formula was intended to be delivered at 180 mL/kg/day versus donor human milk at 200 mL/kg/day.
Outcomes	• NEC reported for complete cohort of 159 infants. • Time to regain birthweight (62 infants) and change in weight (58 infants) and head circumference (48 infants) from the point of regained birthweight until discharge from the neonatal unit or reaching a weight of 2000 g • Validated neurological assessment at 18 months in 122 (85%) of surviving infants, and 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 at 18 months post-term (136 infants)
Notes	*We made a consensus decision to include this study since most infants were very preterm (average 31 weeks' gestation) or VLBW (average 1400 g). 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. **Funding source**: Farley Health Products

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Balanced randomisation sequence was prepared for each centre, within strata defined by birth weight (method of sequence generation not stated)
Allocation concealment (selection bias)	Low risk	Sealed, numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given for in-hospital outcomes. Neurodevelopmental assessments were masked.
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)

Lucas 1984a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	No evidence imbalance in baseline demographics

Lucas 1984b

Study characteristics	
Methods	Randomised controlled trial
Participants	343 infants of birthweight < 1850 g (stratified by birthweight < 1200 g and 1201 g to 1850 g).* Early 1980s in 5 neonatal units in the Anglia region of the UK
Interventions	Donor human milk (N = 170) versus preterm formula (N = 173) as a **supplement** to the mother's own milk
Outcomes	• NEC - suspected and confirmed reported on complete cohort of 343 infants • Time to regain birthweight (132 infants) and rates of change in weight (115 infants), crown-heel length (45 infants), and head circumference (97 infants) from the point of regained birthweight until discharge from the neonatal unit or reaching a weight of 2000 g • 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 at 18 months post-term (302 infants)
Notes	*We made a consensus decision to include this study since most infants were very preterm (average 30 weeks' gestation) or VLBW (average 1380 g). 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. **Funding source**: Farley Health Products

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Balanced randomisation sequence was prepared for each centre, within strata defined by birth weight (method of sequence generation not stated)
Allocation concealment (selection bias)	Low risk	Sealed, numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given

Lucas 1984b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given for in-hospital outcomes. Neurodevelopmental assessments were masked.
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	Low risk	No evidence imbalance in baseline demographics

MILK 2024

Study characteristics	
Methods	Randomised controlled trial
Participants	483 infants of gestational age < 29 weeks or birthweight < 1000 g
Interventions	Preterm formula (N = 244) versus donor human milk (N = 239) given as sole diet or a supplement to maternal breast milk* (with cow's milk-based multinutrient fortifier) until hospital discharge or 120 days after birth *where maternal milk is not available before day 21, or daily expressed maternal milk volume < 85 mL over 5 days between days 7 and 21 after birth
Outcomes	• Bayley Scales of Infant and Toddler Development, Third Edition cognitive score at 22 to 26 months post-term (or death) • NEC • Late-onset infection • Mortality before discharge • In-hospital growth rates (weight, head circumference)
Notes	Intervention given until hospital discharge or 120 days after birth. **Funding source**: Eunice Kennedy Shriver NICHD Neonatal Research Network

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Computer-generated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All parents, caregivers, and investigators masked to group allocation

MILK 2024 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors masked to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete follow up (88%)
Selective reporting (reporting bias)	Low risk	Protocol specified outcomes reported
Other bias	Low risk	No evidence imbalance in baseline demographics

Mills 2024

Study characteristics	
Methods	Randomised controlled trial (3 arms)
Participants	103 very preterm infants
Interventions	• Donor human milk (N = 35), or • Donor human milk with fortifier (N = 34), or • Preterm formula (N = 34)
Outcomes	• Total body adiposity at (quote) "term equivalent" • NEC • Late-onset infection • Mortality before discharge
Notes	www.clinicaltrials.gov/ct2/show/NCT01686477 **Funding source**: unfunded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Computer-generated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, caregivers, and families were masked to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were masked to group allocation
Incomplete outcome data (attrition bias)	Low risk	Complete follow-up

Mills 2024 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	No evidence of imbalance in baseline demographics

O'Connor 2016

Study characteristics	
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. 4 neonatal units in Ontario, Canada, 2010 to 2012
Interventions	Preterm formula (N = 182) versus donor human 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	Quote: "A similar percentage of infants in the donor milk group (28.2%) and formula group (26.9%) were exclusively fed mother's milk" Quote: "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" **Funding source**: Canadian Institutes of Health Research (MOP No. 102638) and the Ontario Ministry of Health and Long-Term Care (grant No. 06465)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	(Quote:)"Computer-driven third-party randomisation service"
Allocation concealment (selection bias)	Low risk	Computer-randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, caregivers, and families were masked to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, caregivers, and families were masked to group allocation
Incomplete outcome data (attrition bias)	Low risk	> 90% assessment for primary outcome

O'Connor 2016 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	No protocol deviations
Other bias	Low risk	No evidence imbalance in baseline demographics

Schanler 2005

Study characteristics

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 human milk (N = 92) given as a supplement to maternal breast milk
Outcomes	• Incidence of late-onset invasive infection and NEC • Duration of hospitalisation • 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 human milk, then a similar advancement and fortification protocol was followed. For all infants, adjustments in milk intake 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 human 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. **Funding source**: US National Institute of Child Health and Human Development and the National Institutes of Health General Clinical Research Center, Baylor College of Medicine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Likely to be computer-generated since the random sequence was (quote:) "an unbalanced blocked design, according to the stratification variables of gestational age and receipt of prenatal steroids"
Allocation concealment (selection bias)	Low risk	(Quote:) Allocation was "performed by the research nurse coordinator with sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded trial

Schanler 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	No evidence imbalance in baseline demographics

Tyson 1983

Study characteristics	
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 human milk (N = 37). The donor human 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. **Funding source**: Robert Wood Johnson Foundation

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

Tyson 1983 *(Continued)*

All outcomes		
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
Other bias	Low risk	No evidence imbalance in baseline demographics

BPD: bronchopulmonary dysplasia; **LBW**: low birthweight; **NEC**: necrotising enterocolitis; **PMA**: postmenstrual age; **SD**: standard deviation; **VLBW**: very low birthweight

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

Study	Reason for exclusion
Brandstetter 2018	Development and proposal of a "decision tree" for prioritising donor human milk use
Castellano 2019	Retrospective cohort study of the impact of 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 human milk
Hair 2014	Randomised trial of human milk "cream" supplementation in VLBW infants
Jarvenpaa 1983	Non-randomised study comparing growth in LBW 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 LBW infants of feeding with formula milk versus "expressed human milk". Many 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 LBW infants fed human milk or formula
Perez 2015	Cohort study of human milk versus formula for LBW infants; not a randomised comparison
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
Raiha 1976	Randomised controlled trial involving preterm infants of birthweight < 2100 g (between 10th and 90th centiles for birthweight). Most infants were not very preterm or VLBW.
Schultz 1980	Randomised controlled trial involving 20 preterm or LBW infants. Most infants were not very preterm or VLBW.
Sullivan 2010	Randomised controlled trial of feeding VLBW infants with formula plus bovine milk-based fortifier versus donor human milk plus human milk-based fortifier; excluded because type of fortifier was co-intervention

Study	Reason for exclusion
Svenningsen 1982	Randomised trial of 2 different formulas versus breast milk in LBW infants; most infants in the breast milk group received their own mother's expressed milk rather than donor human milk (not randomised)
Tewari 2018	Randomised trial of early versus late feeding of very preterm infants with maternal or donor human milk

LBW: low birthweight; **VLBW**: very low birthweight

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

NCT01232725

Study name	Donor human milk and neurodevelopmental outcomes in very low birthweight (VLBW) infants
Methods	Randomised controlled trial
Participants	121 VLBW infants. 2 neonatal units in the 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)

NCT01390753

Study name	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 VLBW infants
Interventions	Donor human milk and preterm formula versus preterm formula alone
Outcomes	Incidence of respiratory infections in infancy
Starting date	2012
Contact information	Fernando Pedro Polack; malinez@infant.org.ar
Notes	

VLBW: very low birthweight

DATA AND ANALYSES

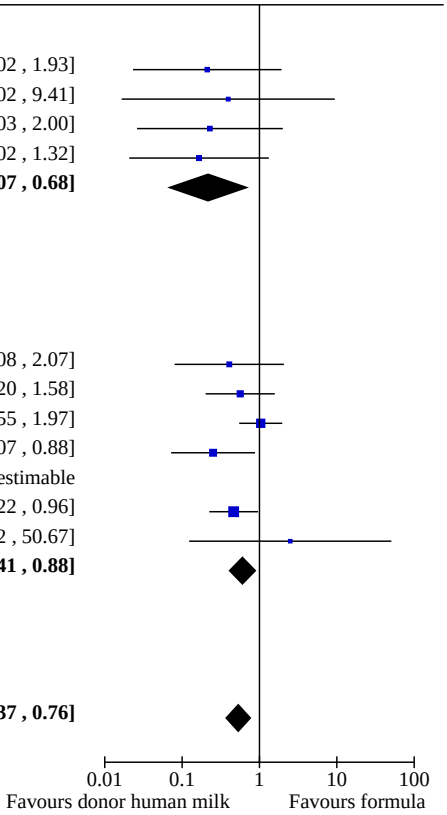
Comparison 1. Donor human milk versus formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Necrotising enterocolitis	11	2261	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.37, 0.76]
1.1.1 Sole diet	4	360	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.68]
1.1.2 Supplement to maternal milk	7	1901	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.41, 0.88]
1.2 Late-onset invasive infection	7	1611	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.95, 1.31]
1.2.1 Sole diet	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.47, 1.03]
1.2.2 Supplement to maternal milk	6	1558	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.99, 1.39]
1.3 All-cause mortality	9	2116	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.31]
1.3.1 Sole diet	2	212	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.25, 1.41]
1.3.2 Supplement to maternal milk	7	1904	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.79, 1.41]
1.4 In-hospital rate of weight gain (g/kg/day) until term equivalent	9	1360	Mean Difference (IV, Fixed, 95% CI)	-3.55 [-4.21, -2.89]
1.4.1 Sole diet	5	275	Mean Difference (IV, Fixed, 95% CI)	-6.01 [-7.13, -4.90]
1.4.2 Supplement to maternal milk	4	1085	Mean Difference (IV, Fixed, 95% CI)	-2.25 [-3.06, -1.43]
1.5 In-hospital rate of head circumference growth (mm/week) until term equivalent	9	1261	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.01, -0.36]
1.5.1 Sole diet	5	283	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-2.08, -0.95]
1.5.2 Supplement	4	978	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.67, 0.12]
1.6 Weight (kg) at 18 months post-term	2	438	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.35, 0.15]
1.6.1 Sole diet	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.57, 0.37]
1.6.2 Supplement	1	302	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.39, 0.19]
1.7 Head circumference (cm) at 18 months post-term	2	438	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.39, 0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Sole diet	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.64, 0.44]
1.7.2 Supplement	1	302	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.45, 0.25]
1.8 Bayley Mental Development Index at 18 months	2	387	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-5.09, 2.62]
1.8.1 Sole diet	1	114	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-7.21, 6.21]
1.8.2 Supplement	1	273	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-6.31, 3.11]
1.9 Bayley Psychomotor Development Index at 18 months	2	387	Mean Difference (IV, Fixed, 95% CI)	0.32 [-2.79, 3.43]
1.9.1 Sole diet	1	114	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-6.78, 4.38]
1.9.2 Supplement	1	273	Mean Difference (IV, Fixed, 95% CI)	1.00 [-2.74, 4.74]
1.10 Bayley-III	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.10.1 Cognitive	2	722	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-3.43, 1.76]
1.10.2 Language	2	714	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-3.50, 2.43]
1.10.3 Motor	2	714	Mean Difference (IV, Fixed, 95% CI)	-0.92 [-3.84, 2.00]
1.11 Cerebral palsy	4	1124	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.66, 1.46]
1.12 Hearing impairment	1	299	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.29, 3.32]
1.13 Visual impairment	1	299	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.14 Bayley-III score < 70	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.14.1 Cognitive	2	782	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.78, 1.45]
1.14.2 Language	2	778	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.78, 1.28]
1.14.3 Motor	2	779	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.29]
1.15 Neurodevelopmental disability at 18 months	2	400	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.43, 1.60]
1.15.1 Sole diet	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.15, 1.57]
1.15.2 Supplement	1	278	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.48, 2.47]

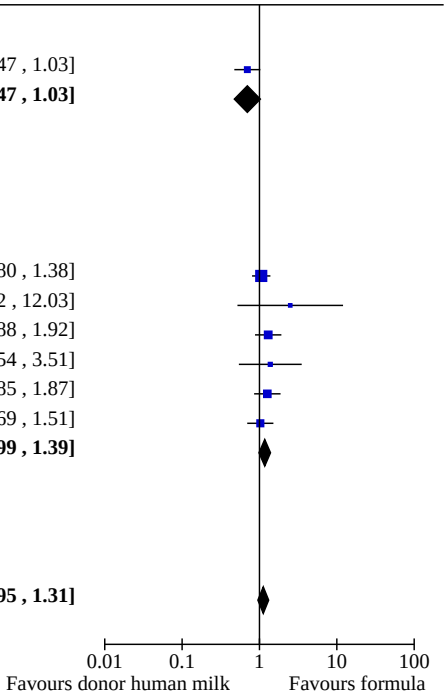
Analysis 1.1. Comparison 1: Donor human milk versus formula, Outcome 1: Necrotising enterocolitis

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Sole diet						
Gross 1983	1	41	3	26	4.6%	0.21 [0.02 , 1.93]
Tyson 1983	0	37	1	44	1.7%	0.39 [0.02 , 9.41]
Lucas 1984a	1	83	4	76	5.2%	0.23 [0.03 , 2.00]
Cristofalo 2013	1	29	5	24	6.8%	0.17 [0.02 , 1.32]
Subtotal (95% CI)		**190**		**170**	**18.3%**	**0.22 [0.07 , 0.68]**
Total events:	3		13			
Heterogeneity: Chi² = 0.20, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.61 (P = 0.009)						
1.1.2 Supplement to maternal milk						
Lucas 1984b	2	170	5	173	6.2%	0.41 [0.08 , 2.07]
Schanler 2005	5	78	10	88	11.7%	0.56 [0.20 , 1.58]
Corpeleijn 2016	17	183	17	190	20.8%	1.04 [0.55 , 1.97]
O'Connor 2016	3	181	12	182	14.9%	0.25 [0.07 , 0.88]
Costa 2018	0	35	0	35		Not estimable
MILK 2024	10	239	22	244	27.2%	0.46 [0.22 , 0.96]
Mills 2024	2	69	0	34	0.8%	2.50 [0.12 , 50.67]
Subtotal (95% CI)		**955**		**946**	**81.7%**	**0.60 [0.41 , 0.88]**
Total events:	39		66			
Heterogeneity: Chi² = 6.25, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 2.59 (P = 0.010)						
Total (95% CI)		**1145**		**1116**	**100.0%**	**0.53 [0.37 , 0.76]**
Total events:	42		79			
Heterogeneity: Chi² = 9.34, df = 9 (P = 0.41); I² = 4%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
Test for subgroup differences: Chi² = 2.75, df = 1 (P = 0.10), I² = 63.6%						



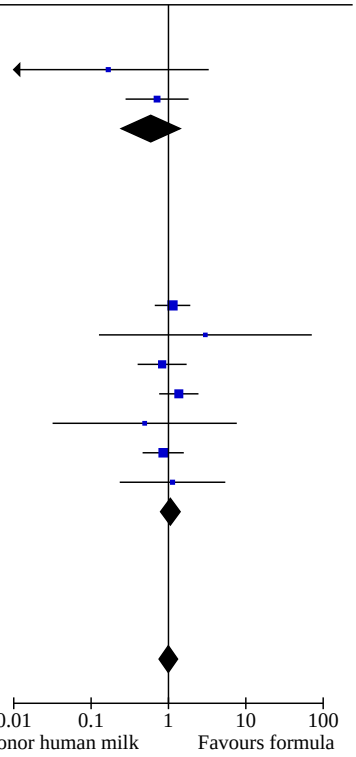
Analysis 1.2. Comparison 1: Donor human milk versus formula, Outcome 2: Late-onset invasive infection

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Sole diet						
Cristofalo 2013	16	29	19	24	10.6%	0.70 [0.47 , 1.03]
Subtotal (95% CI)		**29**		**24**	**10.6%**	**0.70 [0.47 , 1.03]**
Total events:	16		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.2.2 Supplement to maternal milk						
Corpeleijn 2016	67	183	66	190	32.9%	1.05 [0.80 , 1.38]
Costa 2018	5	35	2	35	1.0%	2.50 [0.52 , 12.03]
MILK 2024	47	239	37	244	18.6%	1.30 [0.88 , 1.92]
Mills 2024	14	69	5	34	3.4%	1.38 [0.54 , 3.51]
O'Connor 2016	44	181	35	182	17.7%	1.26 [0.85 , 1.87]
Schanler 2005	30	78	33	88	15.8%	1.03 [0.69 , 1.51]
Subtotal (95% CI)		**785**		**773**	**89.4%**	**1.17 [0.99 , 1.39]**
Total events:	207		178			
Heterogeneity: $Chi^2 = 2.43$, df = 5 (P = 0.79); $I^2 = 0\%$						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**814**		**797**	**100.0%**	**1.12 [0.95 , 1.31]**
Total events:	223		197			
Heterogeneity: $Chi^2 = 8.26$, df = 6 (P = 0.22); $I^2 = 27\%$						
Test for overall effect: Z = 1.39 (P = 0.16)						
Test for subgroup differences: $Chi^2 = 5.76$, df = 1 (P = 0.02), $I^2 = 82.6\%$						



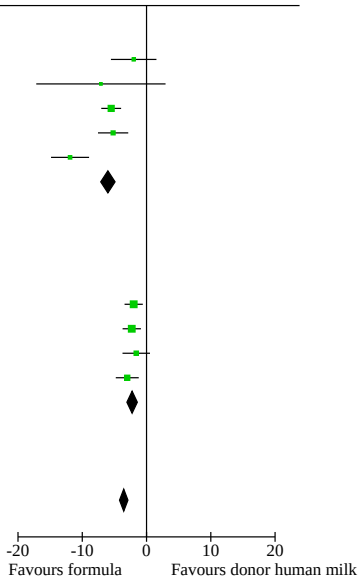
Analysis 1.3. Comparison 1: Donor human milk versus formula, Outcome 3: All-cause mortality

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Sole diet						
Cristofalo 2013	0	29	2	24	3.0%	0.17 [0.01 , 3.31]
Lucas 1984a	7	83	9	76	10.2%	0.71 [0.28 , 1.82]
Subtotal (95% CI)		**112**		**100**	**13.2%**	**0.59 [0.25 , 1.41]**
Total events:	7		11			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.3.2 Supplement to maternal milk						
Corpeleijn 2016	25	183	23	190	24.6%	1.13 [0.67 , 1.91]
Costa 2018	1	35	0	35	0.5%	3.00 [0.13 , 71.22]
Lucas 1984b	12	170	15	176	16.0%	0.83 [0.40 , 1.72]
MILK 2024	24	239	18	244	19.4%	1.36 [0.76 , 2.44]
Mills 2024	1	69	1	34	1.5%	0.49 [0.03 , 7.64]
O'Connor 2016	17	181	20	182	21.7%	0.85 [0.46 , 1.58]
Schanler 2005	3	78	3	88	3.1%	1.13 [0.23 , 5.43]
Subtotal (95% CI)		**955**		**949**	**86.8%**	**1.06 [0.79 , 1.41]**
Total events:	83		80			
Heterogeneity: Chi² = 2.39, df = 6 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.71)						
Total (95% CI)		**1067**		**1049**	**100.0%**	**1.00 [0.76 , 1.31]**
Total events:	90		91			
Heterogeneity: Chi² = 4.41, df = 8 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 1.54, df = 1 (P = 0.21), I² = 35.2%						



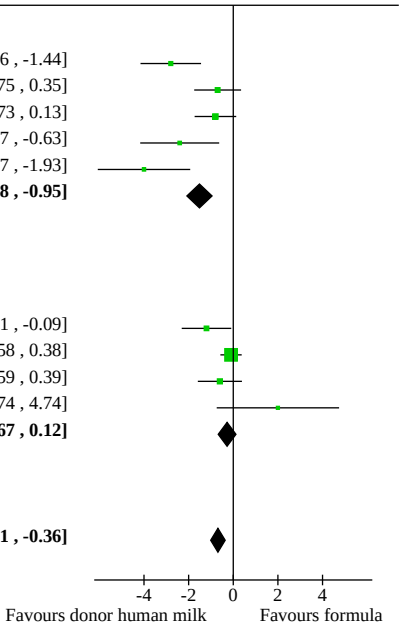
Analysis 1.4. Comparison 1: Donor human milk versus formula, Outcome 4: In-hospital rate of weight gain (g/kg/day) until term equivalent

Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Sole diet								
Cristofalo 2013	15	5.8	29	17	7.1	24	3.4%	-2.00 [-5.54 , 1.54]
Davies 1977	20.5	15.3	14	27.6	11.6	14	0.4%	-7.10 [-17.16 , 2.96]
Gross 1983	14.9	3.2	40	20.4	2.7	20	18.0%	-5.50 [-7.04 , -3.96]
Lucas 1984a	12.8	2.6	28	18	6	30	7.8%	-5.20 [-7.55 , -2.85]
Tyson 1983	12.4	4.8	34	24.3	8.2	42	4.9%	-11.90 [-14.86 , -8.94]
Subtotal (95% CI)			**145**			**130**	**34.6%**	**-6.01 [-7.13 , -4.90]**
Heterogeneity: Chi² = 21.08, df = 4 (P = 0.0003); I² = 81%								
Test for overall effect: Z = 10.57 (P < 0.00001)								
1.4.2 Supplement to maternal milk								
Lucas 1984b	14.3	3.1	59	16.3	4.5	56	21.4%	-2.00 [-3.42 , -0.58]
MILK 2024	22.3	7.8	235	24.6	8.1	243	21.2%	-2.30 [-3.73 , -0.87]
O'Connor 2016	23.9	10	164	25.5	9.7	162	9.4%	-1.60 [-3.74 , 0.54]
Schanler 2005	17.1	5	78	20.1	6.7	88	13.5%	-3.00 [-4.79 , -1.21]
Subtotal (95% CI)			**536**			**549**	**65.4%**	**-2.25 [-3.06 , -1.43]**
Heterogeneity: Chi² = 1.16, df = 3 (P = 0.76); I² = 0%								
Test for overall effect: Z = 5.43 (P < 0.00001)								
Total (95% CI)			**681**			**679**	**100.0%**	**-3.55 [-4.21 , -2.89]**
Heterogeneity: Chi² = 50.92, df = 8 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 10.61 (P < 0.00001)								
Test for subgroup differences: Chi² = 28.69, df = 1 (P < 0.00001), I² = 96.5%								



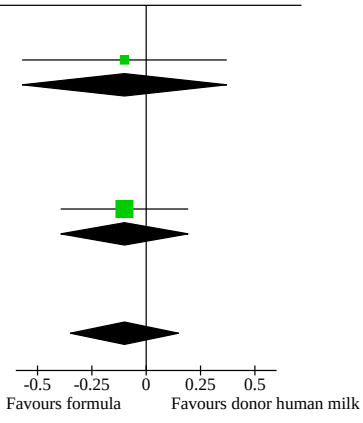
Analysis 1.5. Comparison 1: Donor human milk versus formula, Outcome 5: In-hospital rate of head circumference growth (mm/week) until term equivalent

Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Sole diet								
Cristofalo 2013	8.4	2.1	29	11.2	2.8	24	5.7%	-2.80 [-4.16 , -1.44]
Davies 1977	8.5	2.4	34	9.2	2	34	9.5%	-0.70 [-1.75 , 0.35]
Gross 1983	6.4	1.6	40	7.2	1.8	20	12.1%	-0.80 [-1.73 , 0.13]
Lucas 1984a	7.3	2.4	14	9.7	2.2	12	3.4%	-2.40 [-4.17 , -0.63]
Tyson 1983	7	5	34	11	4	42	2.4%	-4.00 [-6.07 , -1.93]
Subtotal (95% CI)			**151**			**132**	**33.1%**	**-1.51 [-2.08 , -0.95]**
Heterogeneity: Chi² = 14.52, df = 4 (P = 0.006); I² = 72%								
Test for overall effect: Z = 5.27 (P < 0.00001)								
1.5.2 Supplement								
Lucas 1984b	8.4	1.4	25	9.6	2.2	20	8.5%	-1.20 [-2.31 , -0.09]
MILK 2024	7	3	218	7.1	2	223	46.2%	-0.10 [-0.58 , 0.38]
O'Connor 2016	10.1	4.5	164	10.7	4.6	162	10.8%	-0.60 [-1.59 , 0.39]
Schanler 2005	12	8	78	10	10	88	1.4%	2.00 [-0.74 , 4.74]
Subtotal (95% CI)			**485**			**493**	**66.9%**	**-0.28 [-0.67 , 0.12]**
Heterogeneity: Chi² = 6.25, df = 3 (P = 0.10); I² = 52%								
Test for overall effect: Z = 1.37 (P = 0.17)								
Total (95% CI)			**636**			**625**	**100.0%**	**-0.69 [-1.01 , -0.36]**
Heterogeneity: Chi² = 33.18, df = 8 (P < 0.0001); I² = 76%								
Test for overall effect: Z = 4.16 (P < 0.0001)								
Test for subgroup differences: Chi² = 12.41, df = 1 (P = 0.0004), I² = 91.9%								



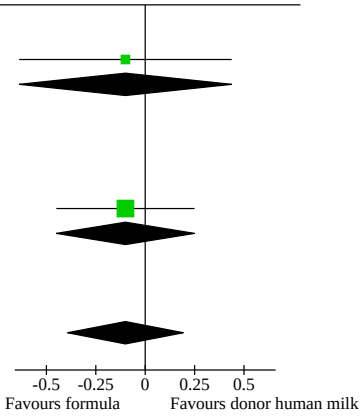
Analysis 1.6. Comparison 1: Donor human milk versus formula, Outcome 6: Weight (kg) at 18 months post-term

Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Sole diet								
Lucas 1984a	9.9	1.5	72	10	1.3	64	28.0%	-0.10 [-0.57 , 0.37]
Subtotal (95% CI)			**72**			**64**	**28.0%**	**-0.10 [-0.57 , 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.68)								
1.6.2 Supplement								
Lucas 1984b	10	1.3	149	10.1	1.3	153	72.0%	-0.10 [-0.39 , 0.19]
Subtotal (95% CI)			**149**			**153**	**72.0%**	**-0.10 [-0.39 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
Total (95% CI)			**221**			**217**	**100.0%**	**-0.10 [-0.35 , 0.15]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.79 (P = 0.43)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								



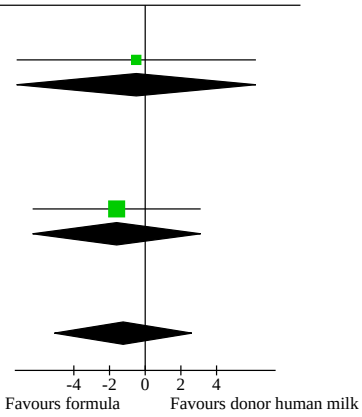
Analysis 1.7. Comparison 1: Donor human milk versus formula, Outcome 7: Head circumference (cm) at 18 months post-term

Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Sole diet								
Lucas 1984a	47.6	1.7	72	47.7	1.5	64	29.7%	-0.10 [-0.64 , 0.44]
Subtotal (95% CI)			**72**			**64**	**29.7%**	**-0.10 [-0.64 , 0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								
1.7.2 Supplement								
Lucas 1984b	48.1	1.5	149	48.2	1.6	153	70.3%	-0.10 [-0.45 , 0.25]
Subtotal (95% CI)			**149**			**153**	**70.3%**	**-0.10 [-0.45 , 0.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.58)								
Total (95% CI)			**221**			**217**	**100.0%**	**-0.10 [-0.39 , 0.19]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.67 (P = 0.50)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								



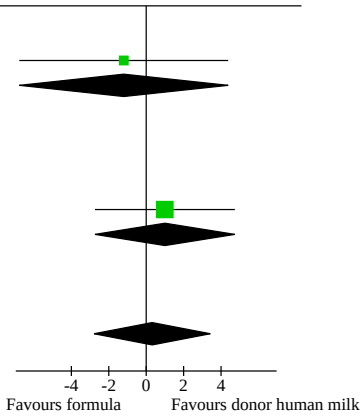
Analysis 1.8. Comparison 1: Donor human milk versus formula, Outcome 8: Bayley Mental Development Index at 18 months

Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 Sole diet								
Lucas 1984a	94.8	16.5	62	95.3	19.5	52	33.0%	-0.50 [-7.21 , 6.21]
Subtotal (95% CI)			**62**			**52**	**33.0%**	**-0.50 [-7.21 , 6.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.15 (P = 0.88)								
1.8.2 Supplement								
Lucas 1984b	102.2	19.7	134	103.8	20	139	67.0%	-1.60 [-6.31 , 3.11]
Subtotal (95% CI)			**134**			**139**	**67.0%**	**-1.60 [-6.31 , 3.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.51)								
Total (95% CI)			**196**			**191**	**100.0%**	**-1.24 [-5.09 , 2.62]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%								
Test for overall effect: Z = 0.63 (P = 0.53)								
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%								



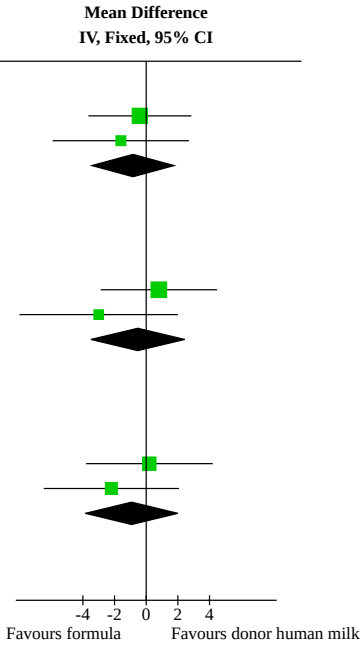
Analysis 1.9. Comparison 1: Donor human milk versus formula, Outcome 9: Bayley Psychomotor Development Index at 18 months

Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Sole diet								
Lucas 1984a	93	14.2	62	94.2	15.9	52	31.0%	-1.20 [-6.78 , 4.38]
Subtotal (95% CI)			**62**			**52**	**31.0%**	**-1.20 [-6.78 , 4.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
1.9.2 Supplement								
Lucas 1984b	95.5	15	134	94.5	16.5	139	69.0%	1.00 [-2.74 , 4.74]
Subtotal (95% CI)			**134**			**139**	**69.0%**	**1.00 [-2.74 , 4.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Total (95% CI)			**196**			**191**	**100.0%**	**0.32 [-2.79 , 3.43]**
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 0.20 (P = 0.84)								
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%								



Analysis 1.10. Comparison 1: Donor human milk versus formula, Outcome 10: Bayley-III

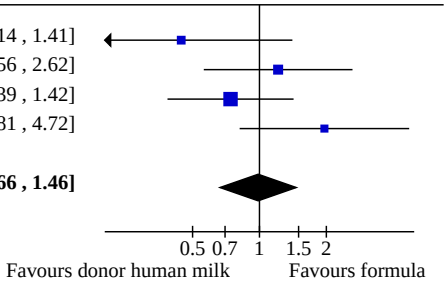
Study or Subgroup	Donor human milk Mean	SD	Total	Formula Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 Cognitive								
MILK 2024	80.7	17.4	206	81.1	16.7	217	63.7%	-0.40 [-3.65 , 2.85]
O'Connor 2016	92.9	19.1	151	94.5	18.9	148	36.3%	-1.60 [-5.91 , 2.71]
Subtotal (95% CI)			**357**			**365**	**100.0%**	**-0.84 [-3.43 , 1.76]**
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 0.63 (P = 0.53)								
1.10.2 Language								
MILK 2024	76.6	19.6	203	75.8	18.6	212	65.0%	0.80 [-2.88 , 4.48]
O'Connor 2016	87.3	21.9	151	90.3	22.3	148	35.0%	-3.00 [-8.01 , 2.01]
Subtotal (95% CI)			**354**			**360**	**100.0%**	**-0.53 [-3.50 , 2.43]**
Heterogeneity: Chi² = 1.44, df = 1 (P = 0.23); I² = 30%								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.10.3 Motor								
MILK 2024	80.3	21.6	202	80.1	19.9	213	53.3%	0.20 [-3.80 , 4.20]
O'Connor 2016	91.8	19.1	151	94	18.6	148	46.7%	-2.20 [-6.47 , 2.07]
Subtotal (95% CI)			**353**			**361**	**100.0%**	**-0.92 [-3.84 , 2.00]**
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%								
Test for overall effect: Z = 0.62 (P = 0.54)								
Test for subgroup differences: Chi² = 0.04, df = 2 (P = 0.98), I² = 0%								



Analysis 1.11. Comparison 1: Donor human milk versus formula, Outcome 11: Cerebral palsy

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lucas 1984a	4	72	8	64	18.5%	0.44 [0.14 , 1.41]
Lucas 1984b	13	149	11	153	23.7%	1.21 [0.56 , 2.62]
MILK 2024	14	188	20	199	42.4%	0.74 [0.39 , 1.42]
O'Connor 2016	14	151	7	148	15.4%	1.96 [0.81 , 4.72]
Total (95% CI)		**560**		**564**	**100.0%**	**0.99 [0.66 , 1.46]**
Total events:	45		46			

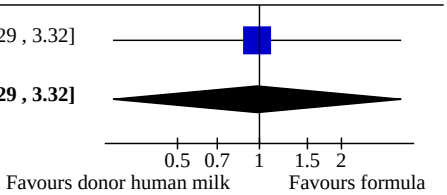
Heterogeneity: Chi² = 5.20, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Donor human milk versus formula, Outcome 12: Hearing impairment

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
O'Connor 2016	5	151	5	148	100.0%	0.98 [0.29 , 3.32]
Total (95% CI)		**151**		**148**	**100.0%**	**0.98 [0.29 , 3.32]**
Total events:	5		5			

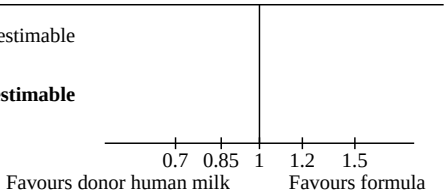
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Donor human milk versus formula, Outcome 13: Visual impairment

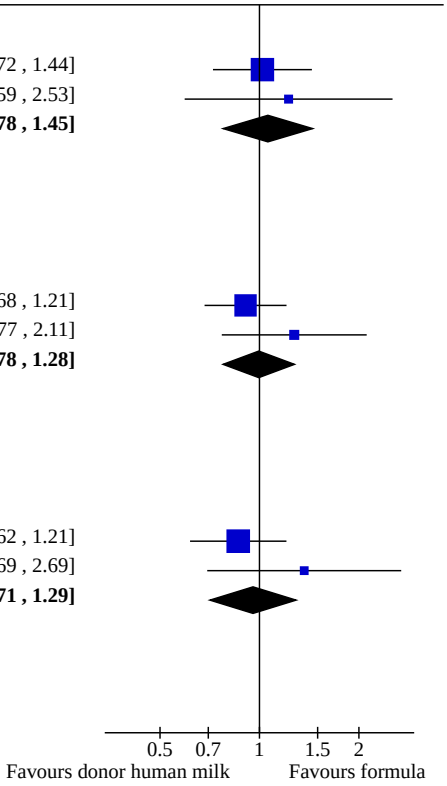
Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
O'Connor 2016	0	151	0	148		Not estimable
Total (95% CI)		**151**		**148**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



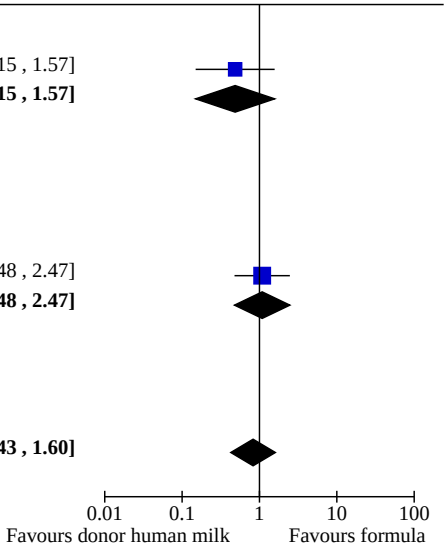
Analysis 1.14. Comparison 1: Donor human milk versus formula, Outcome 14: Bayley-III score < 70

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Cognitive						
MILK 2024	51	239	51	244	80.6%	1.02 [0.72 , 1.44]
O'Connor 2016	15	151	12	148	19.4%	1.23 [0.59 , 2.53]
Subtotal (95% CI)		**390**		**392**	**100.0%**	**1.06 [0.78 , 1.45]**
Total events:	66		63			
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.14.2 Language						
MILK 2024	64	239	72	244	76.1%	0.91 [0.68 , 1.21]
O'Connor 2016	29	150	22	145	23.9%	1.27 [0.77 , 2.11]
Subtotal (95% CI)		**389**		**389**	**100.0%**	**1.00 [0.78 , 1.28]**
Total events:	93		94			
Heterogeneity: Chi² = 1.32, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.14.3 Motor						
MILK 2024	49	239	58	244	81.4%	0.86 [0.62 , 1.21]
O'Connor 2016	18	149	13	147	18.6%	1.37 [0.69 , 2.69]
Subtotal (95% CI)		**388**		**391**	**100.0%**	**0.96 [0.71 , 1.29]**
Total events:	67		71			
Heterogeneity: Chi² = 1.43, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 0.22, df = 2 (P = 0.89), I² = 0%						



Analysis 1.15. Comparison 1: Donor human milk versus formula, Outcome 15: Neurodevelopmental disability at 18 months

Study or Subgroup	Donor human milk Events	Total	Formula Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 Sole diet						
Lucas 1984a	4	66	7	56	42.9%	0.48 [0.15 , 1.57]
Subtotal (95% CI)		**66**		**56**	**42.9%**	**0.48 [0.15 , 1.57]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.15.2 Supplement						
Lucas 1984b	11	140	10	138	57.1%	1.08 [0.48 , 2.47]
Subtotal (95% CI)		**140**		**138**	**57.1%**	**1.08 [0.48 , 2.47]**
Total events:	11		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**206**		**194**	**100.0%**	**0.83 [0.43 , 1.60]**
Total events:	15		17			
Heterogeneity: Chi² = 1.21, df = 1 (P = 0.27); I² = 17%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.2%						



APPENDICES

Appendix 1. Search strategies

Literature searching formula milk v donor human milk – Feb 2023 update

Searched these databases: CINAHL; Cochrane Central Register of Controlled Trials (CENTRAL); Embase; Maternity & Infant Care; MEDLINE

ClinicalTrials.gov and WHO ICTRP

3448 records were retrieved in total and deduplicated against previous search results, leaving 1542 new records for this update (Figure 1).

CINAHL

Via EBSCO

search date 8th February 2024

542 records identified

S1 (MH "Infant, Newborn+") 161,044

S2 TI (neonat* or neo-nat*) OR AB (neonat* or neo-nat*) 85,700

S3 TI (newborn* or new-born* or (newly N1 born*)) OR AB (newborn* or new-born* or (newly N1 born*)) 39,404

S4 TI (preterm or preterms or pre-term or pre-terms) OR AB (preterm or preterms or pre-term or pre-terms) 42,538

S5 TI (preemie* or premie or premies) OR AB (preemie* or premie or premies) 367

S6 TI (prematur* N3 (birth* or born or deliver*)) OR AB (prematur* N3 (birth* or born or deliver*)) 5,751

S7 TI (low N3 (birthweight* or birth-weight*)) OR AB (low N3 (birthweight* or birth-weight*)) 14,832

S8 TI (lbw or vlbw or elbw) OR AB (lbw or vlbw or elbw) 4,112

S9 TI infan* OR AB infan* 140,261

S10 TI (baby or babies) OR AB (baby or babies) 40,184

S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 315,412

S12 (MH "Infant Formula") 4,741

S13 TI ((infant* or pediatric* or paediatric* or baby or babies) N2 formula*) OR AB ((infant* or pediatric* or paediatric* or baby or babies) N2 formula*) 3,160

S14 TI formula* N2 milk OR AB formula* N2 milk 1,596

S15 S12 OR S13 OR S14 6,797

S16 (MH "Milk, Human") 7,948

S17 (MH "Donor Milk") 309

S18 (MH "Milk Banks") 730

S19 TI (milk N2 (bank* or donor* or donat* or shar*)) OR AB (milk N2 (bank* or donor* or donat* or shar*)) 1,239

S20 TI (breastmilk N2 (bank* or donor* or donat* or shar*)) OR AB (breastmilk N2 (bank* or donor* or donat* or shar*)) 53

S21 TI (milk and (DBM or DHM)) OR AB (milk and (DBM or DHM)) 106

S22 S16 OR S17 OR S18 OR S19 OR S20 OR S21 8,480

S23 S11 AND S15 AND S22 1,399

S24 (MH randomized controlled trials+) 142,899

S25 (MH "Double-Blind Studies") 54,812

S26 (MH "Single-Blind Studies") 16,156

S27 (MH "Random Assignment") 83,664

S28 (MH "Pretest-Posttest Design") 55,029

S29 (MH "Cluster Sample") 5,461

S30 TI randomised OR randomized 148,704

S31 AB random* 406,415

S32 TI trial 191,281

S33 MH (sample size) AND AB (assigned OR allocated OR control) 4,474

S34 MH (placebos) 14,359

S35 PT (randomized controlled trial) 156,282

S36 AB (control W5 group) 148,260

S37 MH (crossover design) OR MH (comparative studies) 496,211

S38 AB (cluster W3 RCT) 507

S39 MH animals+ 104,711

S40 MH (animal studies) 157,009

S41 TI (animal model*) 3,953

S42 S39 OR S40 OR S41 252,674

S43 MH (human) 2,783,467

S44 S42 NOT S43 217,916

S45 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 1,050,887

S46 S45 NOT S44 1,002,114

S47 (MH "Control Group") 14,515

S48 TI (group or groups) OR AB (group or groups) 980,050

S49 TI assign* OR AB assign* 97,598

S50 (MH "Multicenter Studies") 359,760

S51 TI (multicentre* or multi-centre* or multicenter* or multi-center*) OR AB (multicentre* or multi-centre* or multicenter* or multi-center*) 74,696

S52 (MH "Controlled Before-After Studies") 236

S53 TI before N3 after OR AB before N3 after 100,341

S54 S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 1,349,834

S55 S54 not S44 1,286,658

S56 S46 OR S55 1,654,313

S57 S23 AND S56 542

Cochrane Central Register of Controlled Trials (CENTRAL)

Via John Wiley's Cochrane Library

search date 8th February 2024

441 records identified

#1 MeSH descriptor: [Infant, Newborn] explode all trees 23835

#2 MeSH descriptor: [Premature Birth] this term only 2438

#3 (neonat* or neo next nat*):ti,ab,kw 28664

#4 (newborn* or new next born* or newly next born*):ti,ab,kw 36314

#5 (preterm or preterms or pre next term or pre next terms):ti,ab,kw 17139

#6 (preemie* or premie or premies):ti,ab,kw 59

#7 (prematur* near/3 (birth* or born or deliver*)):ti,ab,kw 4193

#8 (low near/3 (birthweight* or birth next weight*)):ti,ab,kw 6453

#9 (lbw or vlbw or elbw):ti,ab,kw 1949

#10 infan*:ti,ab,kw 78865

#11 (baby or babies):ti,ab,kw 11449

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 99145

#13 MeSH descriptor: [Infant Formula] this term only 859

#14 ((infant* or pediatric* or paediatric* or baby or babies) near/2 formula*):ti,ab,kw 2569

#15 (formula* near/2 milk):ti,ab,kw 972

#16 #13 or #14 or #15 3085

#17 MeSH descriptor: [Milk, Human] this term only 1496

#18 MeSH descriptor: [Milk Banks] this term only 10

#19 (Milk near/2 (bank* or donor* or donat* or shar*)):ti,ab,kw 274

#20 (Breastmilk near/2 (bank* or donor* or donat* or shar*)):ti,ab,kw 11

#21 (milk and (DBM or DHM)):ti,ab,kw 17

#22 #17 or #18 or #19 or #20 or #21 1677

#23 #12 and #16 and #22 in Trials 441

Embase

Via OVID

search date 8th February 2024

1653 records identified

Database: Embase <1974 to 2024 February 07>

1 newborn/ (614222)

2 prematurity/ (130745)

3 (neonat$ or neo nat$).ti,ab. (417562)

4 (newborn$ or new born$ or newly born$).ti,ab. (229403)

5 (preterm or preterms or pre term or pre terms).ti,ab. (138092)

6 (preemie$ or premie or premies).ti,ab. (365)

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (26729)

8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (53473)

9 (lbw or vlbw or elbw).ti,ab. (14721)

10 infan$.ti,ab. (595121)

11 (baby or babies).ti,ab. (117754)

12 or/1-11 (1347920)

13 artificial milk/ (16903)

14 (infant$ adj2 formula$).ti,ab. (10495)

15 (pediatric adj2 formula$).ti,ab. (1061)

16 (paediatric adj2 formula$).ti,ab. (485)

17 ((baby or babies) adj2 formula$).ti,ab. (479)

18 (formula$ adj2 milk).ti,ab. (5345)

19 or/13-18 (23769)

20 breast milk/ (34670)

21 donor milk/ (675)

22 milk bank/ (490)

23 (Milk adj2 bank$).ti,ab. (1111)

24 (milk adj2 (donor$ or donat$)).ti,ab. (1667)

25 (milk adj2 shar$).ti,ab. (166)

26 (breastmilk adj2 bank$).ti,ab. (16)

27 (breastmilk adj2 (donor$ or donat$)).ti,ab. (71)

28 (breastmilk adj2 shar$).ti,ab. (12)

29 (milk and (DBM or DHM)).ti,ab. (250)

30 or/20-29 (35441)

31 12 and 19 and 30 (5645)

32 exp randomized controlled trial/ (809456)

33 controlled clinical trial/ (472243)

34 Random$.ti,ab,ot. (2032279)

35 randomization/ (99233)

36 intermethod comparison/ (304476)

37 placebo.ti,ab,ot. (372834)

38 (compare or compared or comparison).ti,ot. (617516)

39 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2864684)

40 (open adj label).ti,ab,ot. (113159)

41 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,ot. (279142)

42 double blind procedure/ (215788)

43 parallel group$1.ti,ab,ot. (33031)

44 (crossover or cross over).ti,ab,ot. (126823)

45 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab,ot. (425982)

46 (assigned or allocated).ti,ab,ot. (503524)

47 (controlled adj7 (study or design or trial)).ti,ab,ot. (463261)

48 (volunteer or volunteers).ti,ab,ot. (286749)

49 human experiment/ (654145)

50 trial.ti,ot. (415627)

51 or/32-50 (6491462)

52 (animal/ or nonhuman/) not exp human/ (6576807)

53 51 not 52 (5773052)

54 31 and 53 (1640)

55 limit 31 to conference abstracts (935)

56 51 and 55 (356)

57 54 or 56 (1653)

Maternity & Infant Care

Via OVID

search date 8th February 2024

24 records identified

Database: Maternity & Infant Care Database (MIDIRS) <1971 to January 16, 2024>

1 (neonat$ or neo nat$).ti,ab. (58469)

2 (newborn$ or new born$ or newly born$).ti,ab. (25602)

3 (preterm or preterms or pre term or pre terms).ti,ab. (34961)

4 (preemie$ or premie or premies).ti,ab. (69)

5 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (4882)

6 (low adj3 (birthweight$ or birth weight$)).ti,ab. (13009)

7 (lbw or vlbw or elbw).ti,ab. (3849)

8 infan$.ti,ab. (78796)

9 (baby or babies).ti,ab. (34118)

10 or/1-9 (148466)

11 (infant$ adj2 formula$).ti,ab. (2128)

12 (pediatric adj2 formula$).ti,ab. (6)

13 (paediatric adj2 formula$).ti,ab. (6)

14 ((baby or babies) adj2 formula$).ti,ab. (151)

15 (formula$ adj2 milk).ti,ab. (963)

16 or/11-15 (2853)

17 Human milk.ti,ab. (2616)

18 (Milk adj2 bank$).ti,ab. (491)

19 (milk adj2 (donor$ or donat$)).ti,ab. (667)

20 (milk adj2 shar$).ti,ab. (66)

21 (breastmilk adj2 bank$).ti,ab. (17)

22 (breastmilk adj2 (donor$ or donat$)).ti,ab. (44)

23 (breastmilk adj2 shar$).ti,ab. (10)

24 (milk and (DBM or DHM)).ti,ab. (83)

25 or/17-24 (2917)

26 10 and 16 and 25 (469)

27 limit 26 to randomised controlled trial (24)

MEDLINE

Via OVID

search date 8th February 2024

886 records identified

Database: Ovid MEDLINE(R) ALL <1946 to February 07, 2024>

1 exp Infant, Newborn/ (682553)

2 Premature Birth/ (22419)

3 (neonat$ or neo nat$).ti,ab. (315765)

4 (newborn$ or new born$ or newly born$).ti,ab. (191494)

5 (preterm or preterms or pre term or pre terms).ti,ab. (97875)

6 (preemie$ or premie or premies).ti,ab. (221)

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (18888)

8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (41496)

9 (lbw or vlbw or elbw).ti,ab. (10664)

10 infan$.ti,ab. (509786)

11 (baby or babies).ti,ab. (82609)

12 or/1-11 (1208229)

13 Infant Formula/ (5700)

14 (infant$ adj2 formula$).ti,ab. (8660)

15 (pediatric adj2 formula$).ti,ab. (691)

16 (paediatric adj2 formula$).ti,ab. (293)

17 ((baby or babies) adj2 formula$).ti,ab. (353)

18 (formula$ adj2 milk).ti,ab. (4095)

19 or/13-18 (14515)

20 Milk, Human/ (23133)

21 Milk Banks/ (719)

22 (Milk adj2 bank$).ti,ab. (975)

23 (milk adj2 (donor$ or donat$)).ti,ab. (1296)

24 (milk adj2 shar$).ti,ab. (141)

25 (breastmilk adj2 bank$).ti,ab. (15)

26 (breastmilk adj2 (donor$ or donat$)).ti,ab. (39)

27 (breastmilk adj2 shar$).ti,ab. (10)

28 (milk and (DBM or DHM)).ti,ab. (174)

29 or/20-28 (23671)

30 12 and 19 and 29 (2935)

31 exp randomized controlled trial/ (609858)

32 controlled clinical trial.pt. (95547)

33 randomized.ab. (634050)

34 placebo.ab. (245532)

35 drug therapy.fs. (2664802)

36 randomly.ab. (426634)

37 trial.ab. (684022)

38 groups.ab. (2632566)

39 or/31-38 (5874039)

40 exp animals/ not humans.sh. (5193858)

41 39 not 40 (5135059)

42 30 and 41 (886)

ClinicalTrials.gov

https://clinicaltrials.gov/

Search date: 9th February 2024

Records retrieved: 70

Advanced search, intervention field searched

70 Studies found for: (donation OR donor) AND (milk OR breastmilk)

WHO ICTRP

https://trialsearch.who.int/

Search date: 9th February 2024

Records retrieved: 32

Advanced search screen, recruitment status set to all, search of title field:

"donor milk" OR "milk bank" OR "milk banking" – 32 hits

Appendix 2. RoB 1 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. We assessed blinding 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. We assessed blinding 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 randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We 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 the 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 reported in the

published results. If the study protocol was not published in advance, we contacted the study authors to gain access to the study protocol. We assessed the methods as:

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

7. Other sources of bias. Did the study appear to be free of other problems that could put it at high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design, or if 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; or
- unclear risk.

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

WHAT'S NEW

Date	Event	Description
6 September 2024	New search has been performed	Search updated to 7 February 2024. Two new trials added (MILK 2024; Mills 2024).
6 September 2024	New citation required but conclusions have not changed	The inclusion of two new studies has not changed the conclusion. A new author, Nicholas Meader, joined the review team.

HISTORY

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

Date	Event	Description
8 July 2020	Amended	Typo corrected in Declarations of interest section.
7 August 2019	Amended	Declaration of interest updated for Dr Nicholas D Embleton.
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

WM and Mary Anthony developed the original protocol.

For the 2024 update, WM and NDE screened the search results, performed risk of bias and GRADE assessments, undertook data extraction and analysis, and contributed to the development of the final review. NM conducted statistical testing and regression modelling.

WM, NDE, MQ, and NM approved the final published version of the review.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DECLARATIONS OF INTEREST

MQ was a deputy Co-ordinating Editor for Cochrane Common Mental Disorders; she did not participate in the acceptance or editorial processes for this review.

NDE declares research grants paid to his employer for a trial using commercially prepared, human milk derived products from Prolacta Bioscience, 2017; a grant from Danone Early Life Nutrition for a study on feeding in late and moderately preterm infants, 2018; and a grant for a trial of human milk-derived fortifier from NeoKare, 2022. NDE declares lecture honoraria from Nestle Nutrition Institute donated to charity in 2021 and 2023. NDE declares no financial relationships or benefits. NDE is a member of the UK Association for Milk Banking.

NM has nothing to declare.

WM is a Co-ordinating Editor for Cochrane Neonatal; he did not participate in the acceptance or editorial processes for this review.

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Internal sources

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  Host institution

External sources

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- Vermont Oxford Network, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2024 update we:

- restricted the population of interest to very preterm and very low-birthweight infants in order to enhance applicability to those infants at high risk of developing necrotising enterocolitis and associated complications;
- reversed the order of comparison to donor human milk versus formula (rather than formula versus donor human milk), since donor human milk is regarded as the intervention in most settings and contexts (this reversal is also reflected in the revised title);
- defined the primary outcomes as necrotising enterocolitis, late-onset infection, and all-cause mortality before discharge, as prevention of these outcomes (rather than increasing growth rates) is the main reason for giving donor human milk to very preterm and very low-birthweight infants;
- updated the search strategy;
- assessed funnel plot asymmetry visually and with Harbord's modification of Egger's test for dichotomous outcomes (Harbord 2006);
- updated the risk of bias assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Enteral Nutrition [methods]; *Enterocolitis, Necrotizing [epidemiology] [prevention & control]; Infant Formula; Infant, Extremely Premature; Infant, Premature; Infant, Premature, Diseases [mortality] [prevention & control]; *Infant, Very Low Birth Weight; *Milk, Human; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn