

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

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	2
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	2
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	3
METHODS OF THE REVIEW	3
DESCRIPTION OF STUDIES	4
METHODOLOGICAL QUALITY	4
RESULTS	4
DISCUSSION	9
AUTHORS' CONCLUSIONS	9
POTENTIAL CONFLICT OF INTEREST	9
ACKNOWLEDGEMENTS	9
SOURCES OF SUPPORT	10
REFERENCES	10
TABLES	12
Characteristics of included studies	12
Characteristics of excluded studies	16
ANALYSES	17
Comparison 01. Formula milk versus donor breast milk	17
Comparison 02. Term formula versus donor breast milk	18
Comparison 03. Preterm formula versus donor breast milk	18
Comparison 04. Formula milk given as a sole diet versus donor breast milk given as a sole diet	18
Comparison 05. Formula milk versus donor breast milk given as a supplement to maternal breast milk	18
INDEX TERMS	19
COVER SHEET	19
GRAPHS AND OTHER TABLES	20
Analysis 01.01. Comparison 01 Formula milk versus donor breast milk, Outcome 01 Time to regain birth weight (days from birth)	20
Analysis 01.02. Comparison 01 Formula milk versus donor breast milk, Outcome 02 Short term weight change (g/kg/day)	21
Analysis 01.03. Comparison 01 Formula milk versus donor breast milk, Outcome 03 Short term change in crown-heel length (mm/week)	21
Analysis 01.04. Comparison 01 Formula milk versus donor breast milk, Outcome 04 Short term change in crown-rump length (mm/week)	22
Analysis 01.05. Comparison 01 Formula milk versus donor breast milk, Outcome 05 Short term change in femoral length (mm/week)	22
Analysis 01.06. Comparison 01 Formula milk versus donor breast milk, Outcome 06 Short term change in head circumference (mm/week)	23
Analysis 01.07. Comparison 01 Formula milk versus donor breast milk, Outcome 07 Weight (kg) at 9 months post term	23
Analysis 01.08. Comparison 01 Formula milk versus donor breast milk, Outcome 08 Length (cm) at 9 months post term	24
Analysis 01.09. Comparison 01 Formula milk versus donor breast milk, Outcome 09 Head circumference (cm) at 9 months post term	24
Analysis 01.10. Comparison 01 Formula milk versus donor breast milk, Outcome 10 Weight (kg) at 18 months post term	25
Analysis 01.11. Comparison 01 Formula milk versus donor breast milk, Outcome 11 Length (cm) at 18 months post term	25
Analysis 01.12. Comparison 01 Formula milk versus donor breast milk, Outcome 12 Head circumference (cm) at 18 months post term	26
Analysis 01.13. Comparison 01 Formula milk versus donor breast milk, Outcome 13 Weight (kg) at 7.5-8 years of age	26

Analysis 01.14. Comparison 01 Formula milk versus donor breast milk, Outcome 14 Length (cm) at 7.5-8 years of age	27
Analysis 01.15. Comparison 01 Formula milk versus donor breast milk, Outcome 15 Head circumference (cm) at 7.5-8 years of age	27
Analysis 01.16. Comparison 01 Formula milk versus donor breast milk, Outcome 16 Bayley mental development index at 18 months	28
Analysis 01.17. Comparison 01 Formula milk versus donor breast milk, Outcome 17 Bayley psychomotor development index at 18 months	28
Analysis 01.18. Comparison 01 Formula milk versus donor breast milk, Outcome 18 Neurological impairment at 18 months	29
Analysis 01.19. Comparison 01 Formula milk versus donor breast milk, Outcome 19 Mortality	29
Analysis 01.20. Comparison 01 Formula milk versus donor breast milk, Outcome 20 Necrotising enterocolitis	30
Analysis 01.21. Comparison 01 Formula milk versus donor breast milk, Outcome 21 Suspected necrotising enterocolitis	30
Analysis 01.22. Comparison 01 Formula milk versus donor breast milk, Outcome 22 Feed intolerance or diarrhoea	31
Analysis 01.23. Comparison 01 Formula milk versus donor breast milk, Outcome 23 Incidence of invasive infection	31
Analysis 02.01. Comparison 02 Term formula versus donor breast milk, Outcome 01 Short term weight change (g/kg/day)	32
Analysis 02.02. Comparison 02 Term formula versus donor breast milk, Outcome 02 Short term change in crown-heel length (mm/week)	32
Analysis 02.03. Comparison 02 Term formula versus donor breast milk, Outcome 03 Short term change in head circumference (mm/week)	33
Analysis 02.04. Comparison 02 Term formula versus donor breast milk, Outcome 04 Necrotising enterocolitis	33
Analysis 02.05. Comparison 02 Term formula versus donor breast milk, Outcome 05 Feed intolerance or diarrhoea	34
Analysis 03.01. Comparison 03 Preterm formula versus donor breast milk, Outcome 01 Short term weight change (g/kg/day)	34
Analysis 03.02. Comparison 03 Preterm formula versus donor breast milk, Outcome 02 Short term change in crown-heel length (mm/week)	35
Analysis 03.03. Comparison 03 Preterm formula versus donor breast milk, Outcome 03 Short term change in head circumference (mm/week)	35
Analysis 03.04. Comparison 03 Preterm formula versus donor breast milk, Outcome 04 Necrotising enterocolitis	36
Analysis 03.05. Comparison 03 Preterm formula versus donor breast milk, Outcome 05 Feed intolerance or diarrhoea	36
Analysis 04.01. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 01 Short term weight change (g/kg/day)	37
Analysis 04.02. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 02 Short term change in crown-heel length (mm/week)	37
Analysis 04.03. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 03 Short term change in head circumference (mm/week)	38
Analysis 04.04. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 04 Necrotising enterocolitis	38
Analysis 05.01. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 01 Short term weight change (g/kg/day)	39
Analysis 05.02. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 02 Short term change in crown-heel length (mm/week)	39
Analysis 05.03. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 03 Short term change in head circumference (mm/week)	40
Analysis 05.04. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 04 Mortality	40
Analysis 05.05. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 05 Necrotising enterocolitis	41
Analysis 05.06. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 06 Suspected necrotising enterocolitis	41

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Status: *Updated*

This record should be cited as:

Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD002971. DOI: 10.1002/14651858.CD002971.pub2.

This version first published online: 17 October 2007 in Issue 4, 2007.

Date of most recent substantive amendment: 18 June 2007

ABSTRACT

Background

When sufficient maternal breast milk is not available, the alternative sources of enteral nutrition for preterm or low birth weight infants are donor breast milk or artificial formula milk. Feeding preterm or low birth weight infants with formula milk might increase nutrient input and growth rates. However, since feeding with formula milk may be associated with a higher incidence of feeding intolerance and necrotising enterocolitis, this may adversely affect growth and development.

Objectives

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

Search strategy

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

Selection criteria

Randomised controlled trials comparing feeding with formula milk versus donor breast milk in preterm or low birth weight infants.

Data collection and analysis

Data were extracted using the standard methods of the Cochrane Neonatal Review Group, with separate evaluation of trial quality and data extraction by two reviewer authors, and synthesis of data using relative risk, risk difference and weighted mean difference.

Main results

Eight trials fulfilled the inclusion criteria. Only one trial used nutrient-fortified donor breast milk. Enteral feeding with formula milk compared with donor breast milk resulted in higher rates of growth in the short term. There was no evidence of an effect on long-term growth rates or neurodevelopmental outcomes. Meta-analysis of data from five trials demonstrated a statistically significantly higher incidence of necrotising enterocolitis in the formula fed group: typical relative risk 2.5 (95% confidence interval 1.2, 5.1); typical risk difference: 0.03 (95% confidence interval 0.01, 0.06; number needed to harm: 33 (95% confidence interval 17, 100).

Authors' conclusions

In preterm and low birth weight infants, feeding with formula milk compared with donor breast milk results in a higher rate of short-term growth but also a higher risk of developing necrotising enterocolitis. There are only limited data on the comparison of feeding with formula milk versus nutrient-fortified donor breast milk. This limits the applicability of the findings as nutrient fortification of breast milk is now a common practice in neonatal care. Future trials may compare growth, development and adverse outcomes in infants who receive formula milk versus nutrient-fortified donor breast milk given as a supplement to maternal expressed breast milk or as a sole diet.

PLAIN LANGUAGE SUMMARY

When a mother's own breast milk is not available for feeding her preterm or low birth weight infant, the alternatives are either formula milk or expressed breast milk from a donor mother ("donor breast milk"). Review of eight randomised controlled trials suggests that feeding with formula increases short-term growth rates but is associated with a higher risk of developing the severe gut disorder "necrotising enterocolitis". There is no evidence of an effect on longer-term growth, or on development. Further trials that compare these two strategies are needed. These should probably compare formula milk adapted for preterm infants with donor breast milk supplemented with nutrients.

BACKGROUND

Maternal breast milk is the recommended form of enteral nutrition for preterm or low birth weight infants (AAP 1997). However, sufficient maternal breast milk is not always available. The two common alternatives available for feeding preterm or low birth weight infants are formula milk and donor breast milk.

A variety of formula milks (usually modified cow milk) are available. These vary in energy, protein and mineral content but, broadly, can be considered as:

- (a) "Term" formulae; designed for term infants, based on the composition of mature breast milk. The typical energy content is between about 67 to 70 kilocalories per 100 millilitres.
- (b) "Preterm" formulae; designed to provide nutrient intakes to match intra-uterine accretion rates (Tsang 1993). These are energy-enriched (typically up to about 80 kilocalories per 100 millilitres), and variably protein- and mineral-enriched (Fewtrell 1999).

Expressed breast milk from donor mothers, usually mothers who have delivered at term, generally has a lower content of energy and protein than term formula milk (Gross 1980; Gross 1981). The nutritional quality of donor breast milk may be further compromised by Pasteurisation (Wight 2001). Donor human milk varies with regard to fat, energy and protein content depending upon the stage of lactation at which it is collected. Milk expressed from the donor's lactating breast has a higher energy and protein content than that collected from the contralateral breast ("drip" breast milk) (Lucas 1978).

There is concern that the nutritional requirements of preterm or low birth weight 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. However, a major putative benefit of donor breast milk is that the delivery of immunoprotective and growth factors to the immature gut mucosa may prevent serious adverse outcomes, including necrotising enterocolitis and invasive infection (Beeby 1992; Lucas 1990).

OBJECTIVES

To examine the effect of enteral feeding with formula milk versus donor breast milk on growth, developmental outcomes, and adverse events, including feed tolerance, necrotising enterocolitis, and invasive infection, in preterm or low birth weight infants.

Subgroup analyses:

1. "Term" formula milk (containing up to 72 kilocalories per 100 millilitres) versus donor human milk.
2. "Preterm" formula milk (containing more than 72 kilocalories per 100 millilitres) versus donor human milk.
3. Formula milk given as a sole diet versus donor breast milk given as a sole diet.
4. Formula milk given as a supplement to maternal breast milk versus donor breast milk given as a supplement to maternal breast milk.
5. Formula milk versus nutrient-fortified donor breast milk (defined as supplementation with more than one of the following components: protein, fat, carbohydrate, or minerals).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Controlled trials utilizing either random or quasi-random patient allocation.

Types of participants

Preterm (less than 37 weeks' gestation) or low birth weight (less than 2.5 kilograms) infants.

Types of intervention

Enteral feeding with formula milk versus donor breast milk. The allocated milk feed may form the entire enteral intake or be a supplement to maternal breast milk. Trials in which parenteral nutritional support is available during the period of advancement of enteral feeds are acceptable provided that the groups receive similar treatment other than the type of milk feed.

Types of outcome measures

Primary:

1. Growth:

(i) Rates of weight gain (grams per day, or grams per kilogram per day), linear growth (millimetres per week), head growth (millimetres per week), or skinfold thickness growth (millimetres per week) during the trial period.

(ii) Long-term growth- weight, height, or head circumference (and/or proportion of infants who remain below the tenth percentile for the index population's distribution) assessed at intervals from 6 months of age (corrected for preterm birth), to 18 months, and beyond.

2. Development:

(i) Neurodevelopmental outcomes at greater than, or equal to, 12 months of age (corrected for preterm birth) measured using validated assessment tools.

(ii) Severe neurodevelopmental disability defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70 or more than two standard deviations below the mean), severe auditory impairment (sensorineural deafness requiring (or too severe to (benefit from) hearing aids) or visual impairment (legal blindness). When available, each component was analyzed individually as well as part of the composite outcome.

(iii) Cognitive and educational outcomes at aged more than 5 years old: Intelligence quotient and/or indices of educational achievement measured using a validated assessment tool (including school examination results).

Secondary:

1. Death in the neonatal period (up to 28 days) and death prior to hospital discharge.

2. Necrotising enterocolitis confirmed by at least two of the following features: Abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen; abdominal distension with abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both); blood in stool; lethargy, hypotonia, or apnea (or combination of these); or a diagnosis confirmed at surgery or autopsy.

3. Time after birth to establish full enteral feeding (independently of parenteral nutrition) (days).

4. Feeding intolerance defined as a requirement to cease enteral feeds and commence parenteral nutrition.

5. Incidence of invasive infection as determined by culture of bacteria or fungus from blood, cerebro-spinal fluid, urine, or from a normally sterile body space.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See: Collaborative Review Group search strategy

The standard search strategy of the Cochrane Neonatal Review Group was used. This consisted of searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE (1966- May 2007), and EMBASE (1980 - May 2007), and CINAHL (1982- May 2007). The electronic search used the following text words and MeSH terms: [Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR infan* OR neonat*] AND "Infant-Nutrition"/all subheadings OR Infant Formula OR milk OR formula]. The search outputs were limited with the relevant filters for clinical trials. No language restriction was applied.

References in previous reviews and in studies identified as potentially relevant were examined. The abstracts presented at the annual scientific meetings of the Society for Pediatric Research, the European Society for Pediatric Research from 1980 until 2004 were hand searched. Trials that had been reported only as abstracts were eligible for inclusion if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

METHODS OF THE REVIEW

1. The title and abstract of all studies identified by the above search strategy were screened by two review authors. The full text of any potentially eligible reports was re-assessed and those studies that did not meet all of the inclusion criteria were excluded. Any disagreements were discussed until consensus was achieved.

2. The criteria and standard methods of the Cochrane Neonatal Review Group were used to independently assess the methodological quality of any included trials in terms of allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised individuals. Additional information from the trial authors was requested to clarify methodology and results as necessary.

3. A data collection form was used to aid extraction of relevant information from each included study. Two review authors extracted the data separately. Any disagreements were discussed until consensus was achieved. If data from the trial reports were insufficient, the trialists were contacted for further information.

4. Outcomes for categorical data are presented as relative risk, risk difference, and number needed to treat, with respective 95% confidence intervals. For continuous data, the weighted mean difference with 95% confidence interval was used.

5. The treatment effects of individual trials and heterogeneity between trial results were examined by inspecting the forest plots. The impact of heterogeneity in any meta-analysis was assessed using a measure of the degree of inconsistency in the studies' results (I-squared statistic). If statistical heterogeneity was noted, the possible causes (for example, differences in study quality,

participants, intervention regimens, or outcome assessments) were explored using post-hoc subgroup analyses. A fixed effects model for meta-analyses was used.

DESCRIPTION OF STUDIES

Fourteen trials that appeared to be relevant were identified in the first round of screening. Six studies were excluded and these are detailed in the table, Characteristics of Excluded Studies (Cooper 1984; Jarvenpaa 1983; Narayanan 1982; O'Connor 2003; Putet 1984; Svenningsen 1982). Eight trials were included (Davies 1977; Gross 1983; Lucas 1984a; Lucas 1984b; Raiha 1976; Schanler 2005; Schultz 1980; Tyson 1983; see table, Characteristics of Included Studies). Most of the included studies were undertaken during the late 1970s and early 1980s by investigators attached to neonatal units in Europe and North America. One trial has been undertaken since the year 2000 (Schanler 2005).

Participants

1017 infants in total participated in the included trials. Most participants were clinically stable preterm infants of gestational age less than about 32 weeks', and/or birth weight less than about 1800 grams. Most of the trials specifically excluded infants who were small for gestational age at birth and infants with congenital anomalies, or gastrointestinal or neurological problems.

Interventions

Four trials compared feeding with term formula milk versus donor breast milk (Davies 1977; Gross 1983; Raiha 1976; Schultz 1980). Four trials compared feeding with preterm formula milk versus donor breast milk (Lucas 1984a; Lucas 1984b; Schanler 2005; Tyson 1983). In two of these trials, preterm formula milk or donor breast milk was given as a supplement to maternal breast milk (Lucas 1984b; Schanler 2005). In general, feeds were allocated for several weeks, or until participating infants reached a specified weight (generally above about 2 kg). In all trials, except one (Tyson 1983), the donor breast milk was pasteurised. None of the trials, except the most recent study (Schanler 2005), used nutrient-fortified donor breast milk.

Five trials used donor breast milk collected from mothers who had delivered an infant at term (Davies 1977; Lucas 1984a; Lucas 1984b; Raiha 1976; Schultz 1980). Two of these trials used "drip" breast milk (Lucas 1984a; Lucas 1984b). One trial used preterm milk (Schanler 2005), one trial used both term and preterm milk (Gross 1983) and one trial did not specify the type of donor breast milk (Schanler 2005).

Outcomes

The most commonly reported outcomes were growth parameters during the study period. Most reports also gave information on adverse outcomes, including feed intolerance and necrotising enterocolitis. Only two trials reported long term-growth and neurode-

velopmental outcomes for surviving infants (Lucas 1984a; Lucas 1984b).

METHODOLOGICAL QUALITY

Quality assessments are detailed in the table, Characteristics of Included Studies. In general, methodological quality was fair. The earliest trials did not provide details of the randomisation procedures (Davies 1977; Raiha 1976; Schultz 1980). The other trials used methods of randomisation likely to ensure adequate allocation concealment. Only one of the trials blinded parents, caregivers or assessors prior to hospital discharge (Schanler 2005). In Lucas 1984a and Lucas 1984b, the assessment of long term outcomes in infants was undertaken blind to the dietary intervention. All of the trials achieved complete or near-complete follow up.

RESULTS

FORMULA MILK VS. DONOR BREAST MILK (Comparison 01):

Primary outcomes:

1. Growth (Outcomes 01.01 - 01.15): Time to regain birth weight was reported by five trials. Gross 1983 reported mean time to regain birth weight as statistically significantly lower in the formula fed group, excluding those randomised, but subsequently withdrawn because of feeding intolerance or necrotising enterocolitis (10.3 vs. 15.1 days). Raiha 1976 did not find a statistically significant difference (13.5 vs. 16.3 days). Meta-analysis of these data found that the formula fed group regained birth weight more quickly: Weighted mean difference: -4.0 days (95% confidence interval -5.8, -2.2). Schultz 1980 reported the mean time to regain birth weight as 2.5 weeks in the formula fed group, compared with 1.5 weeks in the human milk fed group. This was stated to be a "non-significant difference". However, standard deviations were not reported and the data could not be included in the meta-analysis. Lucas 1984a reported the median time to regain birth weight as statistically significantly lower in the formula fed infants (10 vs. 16 days). Lucas 1984b did not find a statistically significant difference (13 vs. 15 days). However, in both these trials, standard deviations were not reported and the data were not included in the meta-analysis.

Weight gain rates were reported by eight trials. Davies 1977 did not find a statistically significant difference in the rate of weight gain from birth to two months. Gross 1983 reported a statistically significantly higher rate of weight gain, from the point of regained birth weight until attaining a weight of 1800 grams, in the formula fed group of infants. Lucas 1984a and Lucas 1984b reported statistically significantly higher rates of weight gain from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 grams in the formula fed group of

infants. Raiha 1976 reported a statistically significantly higher rate of weight gain in the formula fed infants from the point of regained birth weight until attaining a weight of 2400 grams. Schanler 2005 found a statistically significantly higher rate of weight gain during the study period in the formula fed group. Schultz 1980 did not find a statistically significant difference in the rate of weight gain from the point of regained birth weight but numerical data were not reported (or available from the authors). Tyson 1983 reported a statistically significantly higher rate of weight gain from the point of entry into the trial (day 10) until day 30 in the formula fed group of infants. Meta-analysis of data from the seven trials that provided numerical data found a statistically significantly higher rate of weight gain in the formula fed group: Weighted mean difference: 2.6 grams per kilogram per day (95% confidence interval 2.0, 3.2). There was statistically significant heterogeneity of effect in this meta-analysis.

Linear growth rates were reported by seven trials. Davies 1977; Gross 1983; and Schanler 2005 did not find any statistically significant difference in the rate of increase in crown-heel length. The other trials reported statistically significantly greater rates of increase in crown-heel length in the formula fed infants (Lucas 1984a; Lucas 1984b; Tyson 1983). Meta-analysis of the data from these six trials demonstrated a statistically significantly greater rate of increase in crown-heel length in the formula fed group: Weighted mean difference: 1.1 mm/week (95% confidence interval 0.6, 1.7). There was statistically significant heterogeneity of effect in this meta-analysis. Raiha 1976 reported statistically significantly greater rates of increase in crown-rump length [mean difference: 0.6 mm/week (95% confidence interval 0.1, 1.1)] and femoral length [mean difference: 0.4 mm/week (95% confidence interval 0.2, 0.6)] in the formula fed infants.

Head growth was reported by six trials. Three trials did not find any statistically significant difference in the rate of increase in occipito-frontal head circumference (Davies 1977; Lucas 1984b; Schanler 2005). Three trials found a statistically significantly greater rate of increase in occipito-frontal head circumference in the formula fed infants (Gross 1983; Lucas 1984a; Tyson 1983). Meta-analysis of the data from these six reports demonstrated a statistically significantly higher rate of increase in occipito-frontal head circumference in the formula fed group: Weighted mean difference: 1.2 mm/week (95% confidence interval 0.7, 1.7). There was statistically significant heterogeneity of effect in this meta-analysis.

Long-term growth data were reported by Lucas 1984a and Lucas 1984b. Neither individual study, nor meta-analyses of data from both studies, found any statistically significant differences in the weight, length, or head circumference at 9 months, 18 months, or 7.5- 8 years post-term.

Development (Outcomes 01.16 - 01.18): Neurodevelopmental outcomes were reported by two trials. Neither Lucas 1984a nor Lucas 1984b, nor a meta-analysis of data from both, found statistically significant differences in Bayley Psychomotor and Mental

Development Indices at 18 months corrected age. Bayley Mental Development Index: Weighted mean difference 1.24 (95% confidence interval -2.6, 5.1). Bayley Psychomotor Development Index: Weighted mean difference -0.3 (95% confidence interval -3.8, 3.9). Long-term neurodevelopmental data were not reported by Gross 1983. However, a subsequent report (only in abstract form) stated that, at 15 months corrected age, both groups had “similar patterns of growth” and “no difference” in Bayley Mental or Psychomotor Developmental Indices. Severe neurodevelopmental disability (Ameil-Tison 1986 classification) was assessed in two trials. Neither Lucas 1984a nor Lucas 1984b, nor a meta-analysis of data from both studies, demonstrated a statistically significant difference in the incidence of neurological impairment at 18 months post term: typical relative risk: 1.2 (95% confidence interval 0.6, 2.3); typical risk difference: -0.02 (95% confidence interval -0.04, 0.17). Cognitive and educational outcomes were not reported by any of the trials.

Secondary outcomes:

Mortality (Outcome 01.19): Data were available from three trials. Two trials reported mortality until 9 months corrected for preterm delivery (Lucas 1984a; Lucas 1984b). The third trial reported mortality until hospital discharge (Schanler 2005). None of the studies found a statistically significant difference. Since it is likely that most infant mortality in this population occurred before hospital discharge, the data from all three trials was combined in a meta-analysis. This analysis did not demonstrate a statistically significant difference: typical relative risk 1.2 (95% confidence interval 0.7, 2.1); typical risk difference: 0.02 (95% confidence interval -0.02, 0.05).

Necrotising enterocolitis (Outcomes 01.20 - 01.21): Reported as an outcome by five trials (Gross 1983; Lucas 1984a; Lucas 1984b; Schanler 2005; Tyson 1983). None found a statistically significant difference. Meta-analysis of data from the five trials demonstrated a statistically significantly higher incidence of necrotising enterocolitis in the formula fed group: typical relative risk 2.5 (95% confidence interval 1.2, 5.1); typical risk difference: 0.03 (95% confidence interval 0.01, 0.06; number needed to harm: 33 (95% confidence interval 17, 100). Lucas 1984a; Lucas 1984b; and Tyson 1983 also reported the incidence of “suspected” necrotising enterocolitis, that is, necrotising enterocolitis including cases with consistent clinical features but without radiological, surgical, or autopsy confirmation. Neither individual study, nor a meta-analysis of data from the three studies, found a statistically significant difference: typical relative risk: 1.4 (95% confidence interval 0.7, 2.7); typical risk difference: 0.02 (95% confidence interval -0.02, 0.06).

Time after birth to establish full enteral feeding: Not reported by any of the included trials. Lucas 1984a reported that significantly more infants in the formula fed group failed to tolerate full enteral feeds by two weeks after birth (25/76 vs. 9/83), and by three weeks after birth (13/76 vs. 4/83).

Feed intolerance (Outcome 01.22): Reported by two trials. Gross 1983 reported a statistically significantly higher rate of feed intolerance in the formula fed group. Tyson 1983 did not detect a significant difference. Meta-analysis demonstrated a statistically significant higher risk of feed intolerance in the formula fed group: typical relative risk: 4.9 (95% confidence interval 1.2, 20.7); typical risk difference: 0.1 (95% confidence interval 0.01, 0.19). Schultz 1980 reported cases of “mild diarrhoea”, but these do not appear to have been clinically important and have not been included in the analysis.

Invasive infection (Outcome 01.23): Reported by one trial. Schanler 2005 did not find a statistically significant difference in the incidence (one or more episodes) of invasive infection: relative risk: 0.97 (95% confidence interval 0.66, 1.44); risk difference: -0.01 (95% confidence interval -0.16, 0.14).

SUBGROUP ANALYSES:

TERM FORMULA MILK VS. DONOR BREAST MILK (Comparison 02):

In all four trials (Davies 1977; Gross 1983; Raiha 1976; Schultz 1980), the formula and donor breast milk was given as a sole diet.

Primary outcomes:

Growth (Outcomes 02.01 - 02.03): Time to regain birth weight was reported by three trials. Meta-analysis of data from two trials found that the formula fed group regained birth weight more quickly: Weighted mean difference: -4.0 days (95% confidence interval -5.8, -2.2) (Gross 1983; Raiha 1976). Schultz 1980 did not find a statistically significant difference but standard deviations were not reported and the data could not be included in the meta-analysis.

Weight gain rates were reported by four trials. Meta-analysis of the data from three trials found that the formula fed group had a statistically significantly greater rate of weight gain: Weighted mean difference: 1.7 grams per kilogram per day (95% confidence interval 1.0, 2.5) (Davies 1977; Gross 1983; Raiha 1976). Schultz 1980 did not find any statistically significant difference but numerical data for inclusion in the meta-analysis were not reported.

Linear growth rates were reported by three trials. Davies 1977 and Gross 1983 did not find statistically significant differences but meta-analysis of the studies demonstrated a statistically significantly greater rate of increase in crown-heel length in the formula fed group: Weighted mean difference: 0.8 mm/week (95% confidence interval 0.1, 1.5). Raiha 1976 reported statistically significantly greater rates of increase in crown-rump length [mean difference: 0.6 mm/week (95% confidence interval 0.1, 1.1)], and femoral length [mean difference: 0.4 mm/week (95% confidence interval 0.2, 0.6)] in the formula fed infants (see 01.05- 01.06).

Head growth was reported by two trials. Meta-analysis demonstrated a statistically significantly higher rate of increase in occipito-frontal head circumference in the formula fed group: Weighted

mean difference: 0.8 mm/week (95% confidence interval 0.1, 1.5) (Davies 1977; Gross 1983).

Long-term growth parameters were not reported by any of the trials.

2. Development: Neurodevelopmental outcomes were not reported by any of the trials.

Secondary outcomes:

Mortality: not reported by any of the trials.

Necrotising enterocolitis (Outcome 02.04): Reported as an outcome by one trial. Gross 1983 did not find a statistically significant difference: relative risk 4.7 (95% confidence interval 0.5, 43.1); typical risk difference: 0.09 (95% confidence interval -0.04, 0.22).

Time after birth to establish full enteral feeding: Not reported by any of the trials.

Feed intolerance (Outcome 02.05): Reported by one trial. Gross 1983 reported a statistically significantly higher rate of feed intolerance in the formula fed group: relative risk: 9.5 (95% confidence interval 1.2, 74.2); risk difference: 0.21 (95% confidence interval 0.04, 0.38).

Invasive infection: Not reported by any of the trials.

SUBGROUP ANALYSES:

PRETERM FORMULA MILK VS. DONOR BREAST MILK(Comparison 03):

These trials varied with respect to the type of donor breast milk and whether the formula or donor breast milk was given as a sole or a supplement to maternal breast milk (Lucas 1984a/Lucas 1984b; Schanler 2005; Tyson 1983).

Primary outcomes:

Growth (Outcomes 03.01 - 03.03): Time to regain birth weight was reported by two trials. Lucas 1984a reported the median time to regain birth weight as statistically significantly lower in the formula fed infants (10 vs. 16 days). Lucas 1984b did not find a statistically significant difference (13 vs. 15 days). Neither trial reported standard deviations so the data could not be included in a meta-analysis.

Weight gain rates were reported in four trials. All of the individual trials, and a meta-analysis of the data, found a statistically significantly greater rate of weight gain in the formula fed group of infants: Weighted mean difference: 3.8 grams per kilogram per day (95% confidence interval 2.9, 4.8) (Tyson 1983; Lucas 1984a; Lucas 1984b; Schanler 2005).

Linear growth rates were reported by four trials. Meta-analysis of the data from the four trials demonstrated a statistically significantly greater rate of increase in crown-heel length in the formula fed group: Weighted mean difference: 1.6 mm/week (95% confidence interval 0.8, 2.4) (Lucas 1984a; Lucas 1984b; Schanler 2005; Tyson 1983).

Head growth was reported by four trials. Meta-analysis of the data from the trials demonstrated a statistically significantly higher rate of increase in occipito-frontal head circumference in the formula fed group: Weighted mean difference: 1.8 mm/week (95% confidence interval 1.1, 2.6) (Lucas 1984b; Lucas 1984a; Schanler 2005; Tyson 1983).

Long-term growth data were reported by two trial (Lucas 1984a; Lucas 1984b; see above).

Development: Neurodevelopmental outcomes were reported by two trials (Lucas 1984a; Lucas 1984b; see above).

Secondary outcomes:

Mortality: Data were available from three trials (Lucas 1984a; Lucas 1984b; Schanler 2005- see 01.19 and above).

Necrotising enterocolitis (Outcome 03.04): Reported as an outcome by four trials (03.07). Meta-analysis of data from the trials demonstrated a borderline statistically significantly higher incidence of necrotising enterocolitis in the formula fed group: typical relative risk 2.26 (95% confidence interval 1.04, 4.90); typical risk difference: 0.03 (95% confidence interval 0.00, 0.06) (Lucas 1984a; Lucas 1984b; Schanler 2005; Tyson 1983).

Time after birth to establish full enteral feeding: Not reported by any of the included trials.

Feed intolerance (Outcome 03.05): Reported by one trial. Tyson 1983 did not detect a significant difference in the incidence of feed intolerance: relative risk: 1.7 (95% confidence interval 0.2, 17.8); risk difference: 0.02 (95% confidence interval -0.06, 0.10).

Invasive infection (see Outcome 01.24): Schanler 2005 did not find a statistically significant difference in the incidence of (one or more episodes of) invasive infection: relative risk: 0.97 (95% confidence interval 0.66, 1.44); risk difference: -0.01 (95% confidence interval -0.16, 0.14).

SUBGROUP ANALYSES:

FORMULA MILK GIVEN AS A SOLE DIET VS. DONOR BREAST MILK GIVEN AS A SOLE DIET (Comparison 04): Davies 1977; Gross 1983; Lucas 1984a; Raiha 1976; Schultz 1980; Tyson 1983):

Primary outcomes:

Growth (Comparisons 04.01 - 04.03): Time to regain birth weight was reported by four trials. Meta-analysis of the two trials found that the formula fed group regained birth weight more quickly: Weighted mean difference: -4.0 days (95% confidence interval -5.8, -2.2) (Gross 1983; Raiha 1976). Schultz 1980 did not find a statistically significant difference. Lucas 1984a reported that the median time to regain birth weight was statistically significantly lower in the formula fed infants. In both these trials, standard deviations were not reported and the data could not be included in the meta-analysis.

Weight gain rates were reported in six trials (Davies 1977; Gross 1983; Lucas 1984a; Raiha 1976; Schultz 1980; Tyson 1983). Meta-analysis of data from five trials that provided numerical data found a statistically significantly higher rate of weight gain in the formula fed group: Weighted mean difference: 2.7 grams per kilogram per day (95% confidence interval 2.0, 3.4). Schultz 1980 did not find any statistically significant difference in the rate of weight gain but numerical data were not reported.

Linear growth rates were reported by five trials. Meta-analysis of the data from four of these trials demonstrated a statistically significantly greater rate of increase in crown-heel length in the formula fed group Weighted mean difference: 1.3 mm/week (95% confidence interval 0.7, 1.9) (Davies 1977; Gross 1983; Lucas 1984a; Tyson 1983). Raiha 1976 reported statistically significantly greater rates of increase in crown-rump length [mean difference: 0.6 mm/week (95% confidence interval 0.1, 1.1)] and femoral length [mean difference: 0.4 mm/week (95% confidence interval 0.2, 0.6)] in the formula fed infants.

Head growth was reported by four trials: Meta-analysis of the data from these four trials demonstrated a statistically significantly higher rate of increase in occipito-frontal head circumference in the formula fed group: Weighted mean difference: 1.4 mm/week (95% confidence interval 0.9, 2.0) (Davies 1977; Gross 1983; Lucas 1984a; Tyson 1983).

Long-term growth data were reported by Lucas 1984a. The trial did not detect any statistically significant differences in the weight, length, or head circumference at 9 months, 18 months, or 7.5- 8 years post-term.

Development: Neurodevelopmental outcomes were reported by Lucas 1984a (see above). The trial did not find any statistically significant differences in Bayley Psychomotor and Mental Development Indices, nor in the incidence of neurological impairment, at 18 months corrected age. Numerical data on long term neurodevelopment were not reported by Gross 1983. At 15 months corrected age, both groups had "similar patterns of growth" and "no difference" in Bayley Mental or Psychomotor Developmental Indices. Cognitive and educational outcomes were not reported by any of the trials.

Secondary outcomes:

Mortality: Data were available from one trial (see above). Lucas 1984a did not find a statistically significant difference: relative risk 1.4 (95% confidence interval 0.5, 3.6); risk difference: 0.03 (95% confidence interval -0.06, 0.13)

Necrotising enterocolitis (Outcome 04.03): Reported by three trials. Meta-analysis of data demonstrated a borderline statistically significantly higher incidence of necrotising enterocolitis in the formula fed group: typical relative risk 4.0 (95% confidence interval 1.0, 16.2); typical risk difference: 0.05 (95% confidence interval 0.00, 0.09) (Gross 1983; Lucas 1984a; Tyson 1983).

Time after birth to establish full enteral feeding: Not reported by any of the included trials. Lucas 1984a reported that significantly more infants in the formula fed group failed to tolerate full enteral feeds by two weeks after birth (25/76 vs. 9/83), and by three weeks after birth (13/76 vs. 4/83).

Feed intolerance: Reported by two trials (see above). Gross 1983 reported a statistically significantly higher rate of feed intolerance in the formula fed group. Tyson 1983 did not detect a significant difference. Meta-analysis demonstrated a statistically significant higher risk of feed intolerance in the formula fed group: typical relative risk: 4.9 (95% confidence interval 1.2, 20.7); typical risk difference: 0.1 (95% confidence interval 0.01, 0.19).

Invasive infection: Not reported by any of the trials.

SUBGROUP ANALYSES:

FORMULA MILK GIVEN AS A SUPPLEMENT TO MATERNAL BREAST MILK VS. DONOR BREAST MILK GIVEN AS A SUPPLEMENT TO MATERNAL BREAST MILK(Comparison 05):

Both trials used preterm formula (Lucas 1984b; Schanler 2005).

Primary outcomes:

Growth (Outcomes 05.01 - 05.03): Time to regain birth weight was reported by one trial. Lucas 1984b did not find a statistically significant difference (13 vs. 15 days). Standard deviations were not reported.

Weight gain rates were reported in both trials. Lucas 1984b and Schanler 2005 both reported a statistically significantly greater rate of weight gain in the formula fed group of infants: Weighted mean difference: 2.4 grams per kilogram per day (95% confidence interval 1.3, 3.5).

Linear growth rates were reported in both trials. Lucas 1984b reported statistically significantly greater rates of increase in crown-heel length in the formula fed infants. Schanler 2005 did not find any statistically significant difference. Meta-analysis of the data from the two trials did not find a statistically significant difference: Weighted mean difference: 0.7 mm/week (95% confidence interval -0.3, 1.8).

Head growth was reported by two trials. Neither Lucas 1984b nor Schanler 2005, nor meta-analysis of the two trials found a statistically significant difference: Weighted mean difference: 0.6 mm/week (95% confidence interval -0.4, 1.6).

Long-term growth data were reported by one trial (see above). Lucas 1984b did not find any statistically significant differences in the weight, length, or head circumference at 9 months, 18 months, or 7.5- 8 years post-term.

Development: Neurodevelopmental outcomes were reported by one trial (see above). Lucas 1984b did not find any statistically significant differences in Bayley Psychomotor and Mental Development

Indices or in the incidence of neurological impairment at 18 months corrected age.

Secondary outcomes:

Mortality (Outcome 05.04): Data were available from two trials. Neither Lucas 1984b nor Schanler 2005, nor meta-analysis of the two trials found a statistically significant difference: typical relative risk 1.2 (95% confidence interval 0.6, 2.2); typical risk difference: 0.01 (95% confidence interval -0.03, 0.05).

Necrotising enterocolitis (see Outcomes 03.05- 03.06): Reported as an outcome by two trials. Neither Lucas 1984b nor Schanler 2005, nor meta-analysis of the two trials found a statistically significant difference: typical relative risk 2.0 (95% confidence interval 0.8, 4.7); typical risk difference: 0.03 (95% confidence interval -0.01, 0.06). One trial also reported incidences including cases of "suspected" necrotising enterocolitis. Lucas 1984b did not find a statistically significant difference: relative risk 1.1 (95% confidence interval 0.5, 2.4); risk difference: 0.00 (95% confidence interval -0.05, 0.06).

Time after birth to establish full enteral feeding: Not reported by any of the included trials.

Feed intolerance: Not reported by any of the included trials.

Invasive infection: Reported by one trial (Schanler 2005; see above).

SUBGROUP ANALYSES:

FORMULA MILK VS. NUTRIENT-FORTIFIED DONOR BREAST MILK:

Schanler 2005)

As only one trial is included in this analysis, a separate comparison was not created. Data discussed below is derived from the report of the individual trial in Table 01.

Primary outcomes:

Growth: Not reported.

Development: Not reported.

Secondary outcomes:

Mortality:Schanler 2005 did not find a statistically significant difference: relative risk 0.9 (95% confidence interval 0.2, 4.3); risk difference: 0.00 (95% confidence interval -0.06, 0.05).

Necrotising enterocolitis. Schanler 2005 did not find a statistically significant difference: relative risk 1.8 (95% confidence interval 0.6, 5.0); risk difference: 0.05 (95% confidence interval -0.04, 0.14).

Time after birth to establish full enteral feeding: Not reported.

Feed intolerance: Not reported.

Invasive infection: Schanler 2005 did not find a statistically significant difference in the incidence of (one or more episodes of) invasive infection: relative risk: 0.97 (95% confidence interval 0.66, 1.44); risk difference: -0.01 (95% confidence interval -0.16, 0.14).

DISCUSSION

These data suggest that preterm or low birth weight infants who receive formula milk regain birth weight earlier and have higher short-term rates of weight gain, linear growth, and head growth than infants who receive donor breast milk. Subgroup analyses found that studies that used preterm formula milk had greater effects on growth parameters than those that used term formula compared with donor breast milk. However, follow-up of the infants who participated in the two largest trials did not find a significant effect on long-term growth parameters or neurodevelopmental outcomes (Lucas 1984a; Lucas 1984b).

These findings should be interpreted with caution. Substantial heterogeneity between the studies limits the validity of the pooled estimates of effect size. The trials used different inclusion criteria and varied in terms of the type of formula and donor breast milk used. Furthermore, all of the studies, except one (Schanler 2005), used donor breast milk without any additional nutrient fortification. This limits the applicability of the findings to current practice where nutrient fortification of breast milk is commonly undertaken (Kuschel 1999; Kuschel 2000a; Kuschel 2000b; Kuschel 2004). Evidence exists that supplementation of human milk with nutrient fortifiers increases short term growth rates, but does not appear to affect growth beyond infancy (Kuschel 2004).

Meta-analysis of data from five trials suggests that feeding with formula milk significantly increases the risk of developing necrotising enterocolitis. The observed effect sizes were similar across the five studies, and there was no statistical evidence of heterogeneity. The pooled estimate suggests that one extra case of necrotising enterocolitis will occur in every 33 infants who receive formula milk. However, none of the trials were able to blind caregivers and assessors to the intervention. This methodological weakness may have resulted in surveillance and ascertainment biases that contributed to the higher rate of detection of necrotising enterocolitis in formula-fed infants. It is also unclear whether this putative benefit of donor breast milk exists when given as a supplement to maternal breast milk rather than as a sole diet. Meta-analysis of the two trials that examined this comparison did not detect a statistically significant effect (Lucas 1984b; Schanler 2005). Finally, caution should be exercised in applying these data as growth-restricted preterm infants (or sick infants) since this population, although at high risk of developing necrotising enterocolitis, were excluded from the included trials (Dorling 2006).

The data in this review are from trials undertaken in resource-rich countries. In resource-poor countries, where the risk of infection

in the neonatal period is much higher, the anti-infective properties of breast milk may confer advantages that outweigh the lower rate of short-term growth. In India, a randomised trial in low birth weight infants “at risk of infection” found that serious infections (diarrhoea, pneumonia, septicaemia) were statistically significantly less common in infants allocated to received “expressed human milk” versus formula milk (Narayanan 1982). “Expressed human milk” in this study referred to a mixture of maternal and donor breast milk. As these could not be separated into sub-groups, the data were not included in the review.

AUTHORS’ CONCLUSIONS

Implications for practice

Feeding with formula milk, compared with donor breast milk, leads to higher rates of short-term growth in preterm or low birth weight infants, but is associated with an increased risk of developing necrotising enterocolitis. There are only limited data from randomised trials on the comparison of feeding with formula milk versus nutrient-fortified human milk. This limits the implications for practice of this review as nutrient fortification of human milk is now a common practice in neonatal care.

Implications for research

Further randomised controlled trials are needed to assess the effect of feeding preterm or low birth weight infants with formula milk versus donor breast milk in situations where the expressed breast milk of the infant’s mother is not consistently available. Future studies should probably compare enteral feeding with formula milk versus nutrient-fortified donor breast milk in a population of infants at increased risk of necrotising enterocolitis, such as very low birth weight infants. Separate comparisons of formula versus donor breast milk as supplements to maternal expressed breast milk and as sole diets are warranted, since their effects may vary. Trials should attempt to ensure that carers and assessors are blind to the intervention. Although more easily achievable for the longer term assessments, this is also important with regard to ascertainment of adverse events, such as feed intolerance and necrotising enterocolitis, where the threshold for investigation or diagnosis may be affected by knowledge of the intervention.

POTENTIAL CONFLICT OF INTEREST

None

ACKNOWLEDGEMENTS

The UK National Perinatal Epidemiology Unit receives funding from the UK Department of Health. The views expressed in this

publication are those of the authors and not necessarily those of the Department of Health.

SOURCES OF SUPPORT

External sources of support

- Department of Health UK
- Royal College of Paediatrics and Child Health UK
- Tenovus, Scotland UK

Internal sources of support

- ANU Medical School AUSTRALIA
- National Perinatal Epidemiology Unit UK

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*Indicates the major publication for the study

T A B L E S**Characteristics of included studies**

Study	Davies 1977
Methods	1. Blinding of randomisation: Can't tell 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: No
Participants	68 preterm infants: 28-36 weeks in two strata. Exclusions: multiple births, congenital abnormalities and chromosomal disorders, congenital infection. Growth restricted infants (<5th percentile) may also have been excluded. Department of Child Health, University Hospital of Wales, Cardiff. 1972- 73.

Characteristics of included studies (Continued)

Interventions	Term formula milk (N= 34) versus unfortified, Pasteurised donor breast milk (N= 34). Assigned from birth for 2 months.
Outcomes	Rates of weight gain, increase in head circumference and length from birth until 1 month and from 1 month until 2 months.
Notes	Infants of mothers who wished to breastfeed were initially given expressed breast milk if unable to feed naturally. There were only two such infants, their feeding group was not specified and the results for these infants are not presented separately in the paper. Given that this applies to only two out of 68 infants, we have included this study in the review.
Allocation concealment	B – Unclear

Study **Gross 1983**

Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: No 4. Blinding of outcome measurement: Can't tell
Participants	67 preterm infants (27-33 weeks). Birth weight <1600g. Excluded if "congenital anomaly or major disease". Dept of Pediatrics, Duke University, USA. 1980- 82.
Interventions	Term formula milk (N= 26) versus unfortified, Pasteurised donor breast milk (N=41). Feeds were assigned until the infant reached a weight of 1800g or until withdrawn from the study because of feed intolerance or necrotising enterocolitis.
Outcomes	Time to regain birth weight. Mean daily gain in weight, length and head circumference, from regaining birth weight until reaching 1800g. Data on adverse events can be determined although these were not primary end-points of the study.
Notes	Although the report gave information on adverse outcomes, the seven affected infants were withdrawn from the study and not included in the analyses of growth rates. Therefore, growth data are reported for 20 infants in each arm of the trial.
Allocation concealment	A – Adequate

Study **Lucas 1984a**

Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	159 infants of birth weight <1850g. Stratified by birth weight <1200g and 1201- 1850g. Infants with congenital abnormalities excluded. Infants with intra-uterine growth restriction not excluded. Study undertaken in the early 1980's in neonatal units in Anglia region of the UK.
Interventions	Preterm formula milk (N= 76) versus donor (mainly "drip") breast milk (N= 83). The formula was intended to be delivered at 180 ml/kg/day versus the breast milk at 200 ml/kg/day. Feeds were assigned until the infant reached a weight of 2000 g or until discharge from the neonatal unit.
Outcomes	Short term outcomes: Time to regain birth weight (62 infants). Rates of change in weight (58 infants), crown-heel length (26 infants) and head circumference (48 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g. Incidence of necrotising enterocolitis- suspected and confirmed reported on complete cohort of 159 infants. Longer term outcomes: Validated neurological assessment at 18 months in 122 (85%) of surviving infants.

Characteristics of included studies (Continued)

	Bayley mental development index and psychomotor development index at 18 months, corrected for preterm gestation, in 114 (94%) of surviving infants suitable for the assessment. Growth performance in surviving infants (weight, length and head circumference) at 9 months (110 infants), 18 months (136 infants), and 7.5- 8 years (130 infants) post term.
Notes	The first “interim” report provided data on short term growth outcomes in a pre-defined 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.
Allocation concealment	A – Adequate

Study	Lucas 1984b
Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	343 infants of birth weight <1850 g. Stratified by birth weight <1200g and 1201- 1850g. Infants with congenital abnormalities excluded. Infants with intra-uterine growth restriction not excluded. Study undertaken in the early 1980's in neonatal units in Anglia region of the UK.
Interventions	Preterm formula milk (N= 173) versus banked donor breast milk (N= 170) as a supplement to the mother's own breast milk.
Outcomes	Short term outcomes: Time to regain birth weight (132 infants). Rates of change in weight (115 infants), crown-heel length (45 infants) and head circumference (97 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g. Incidence of necrotising enterocolitis- suspected and confirmed reported on complete cohort of 343 infants. Longer term outcomes: Validated neurological assessment, at 18 months, in 278 (88%) of surviving infants. Bayley mental development index and psychomotor development index at 18 months, corrected for preterm gestation, in 273 (96%) of surviving infants suitable for the assessment. Growth performance in surviving infants (weight, length and head circumference) at 9 months (259 infants), 18 months (302 infants), and 7.5- 8 years (290 infants) post term.
Notes	The first “interim” report provided data on short term growth outcomes in a pre-defined 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 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.
Allocation concealment	A – Adequate

Study	Raiha 1976
Methods	1. Blinding of randomisation: Yes (only for formula milk groups) 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell

Characteristics of included studies (Continued)

Participants	106 preterm infants of birth weight less than 2100g, but between 10th and 90th centiles for birth weight. Infants excluded if evidence of "physical abnormality or obvious disease". Premature Unit, Helsinki University Children's Hospital. 1972 to 1975.
Interventions	Term formula milk (N= 84) versus unfortified donor breast milk (N= 22). Feeds continued until a weight of 2.4 kg was attained or until infants were withdrawn from the study because of a "medical complication".
Outcomes	Time, from birth, to regain birth weight. Rate of weight change from birth and from point of regained birth weight.
Notes	Allocation to the formula milks was undertaken using a random sequence of four numbers, but every fifth infant was allocated to receive term human milk, so allocation concealment may have been sub-optimal. Donor breast milk was given at a 170 mL/kg/day, compared with formula at 150 mL/kg/day, "in order to achieve equivalent calorie inputs". Donor breast milk fed infants were also given supplemental vitamins.
Allocation concealment	B – Unclear

Study Schanler 2005

Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	173 infants of gestational age less than 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 milk (N= 81) versus unfortified donor breast milk (N=92) given as a supplement to maternal breast milk.
Outcomes	Incidence of late-onset invasive infection and/or necrotising enterocolitis, duration of hospitalisation and growth during the study period (weight gain, head circumference increment, and length increment).
Notes	Participating infants received small quantities (20 ml per kg per day) of their own mother's milk during the first week after birth and continued for 3-5 days before the volume was advanced. Milk intake was increased by 20 ml per kg per day to 100 ml per kg at which time human milk fortifier was added. Subsequently the volume of fortified human milk was advanced by 20 ml/kg per day until 160 mL/kg per day was achieved. If no mother's milk was available and the baby was assigned to donor breast milk then a similar advancement and fortification protocol was followed. For all infants, adjustments in milk intake between 160 and 200 mL/kg per day were recommended to ensure an average weekly weight gain of at least 15 g/kg per day. 17 enrolled infants were switched from donor breast milk to preterm formula because of poor weight gain but all of the 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.
Allocation concealment	A – Adequate

Study Schultz 1980

Methods	1. Blinding of randomisation: Can't tell 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	20 preterm or low birth weight infants; all infants to be "physically normal with no further signs of disease; no further details published. Department of Paediatrics, University Medical School, Pecs, Hungary, prior to 1980.
Interventions	Term formula milk (N= 10) versus donor breast milk (N= 10) for at least four weeks from birth.
Outcomes	Time, from birth, to regain birth weight (mean but no standard deviation reported).

Mean weight change from birth and from regaining birth weight calculable from graph but no SD.

Notes	
Allocation concealment B – Unclear	
Study	Tyson 1983
Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell for growth assessments, yes for Brazelton score.
Participants	81 very low birth weight infants, excluding infants with “any significant illness” or those who required ventilatory support at day 10. Parklands memorial Hospital, Dallas, USA. Early 1980s.
Interventions	Preterm formula milk (N= 44) versus donor breast milk (N= 37). The donor breast milk was not Pasteurised. Feeds were allocated on the tenth 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 tenth until the thirtieth day of life were reported.
Notes	The feeds were not allocated until the tenth day after birth in order to avoid the use of protein-enriched formula “when active growth was unlikely”. In the first nine 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 necrotising enterocolitis, the five affected infants were withdrawn from the study and not included in the analyses of growth rates.
Allocation concealment A – Adequate	

Characteristics of excluded studies

Study	Reason for exclusion
Cooper 1984	Cooper 1984 measured growth and adverse events in preterm infants fed preterm formula or donor breast milk, but for most participants the feeding group was not allocated randomly.
Jarvenpaa 1983	Jarvenpaa 1983 compared growth in low birth weight infants fed formula versus breast milk. However, the allocation was not random since those infants whose mothers chose to provide their own milk were selectively assigned to the human milk group.
Narayanan 1982	Narayanan 1982 reported a block randomised trial in low birth weight infants of feeding with formula milk versus “expressed human milk”, the latter being a mixture of preterm and term human milk. The randomised blocked design was followed strictly at first, but in the second year, many of the low birth weight infants were allocated to one of the human milk groups (rather than the formula group). Hence, the data for year 1 are completely random (all 4 groups can be compared and be included in our review), but the data for year 2 (and beyond) were not completely random (and should not be included). The authors reported that the results in the random and “non-random” phases were similar and therefore presented the combined results. The authors have been contacted to see if the results for year 1 are available separately.
O'Connor 2003	O'Connor 2003 compared growth, feeding tolerance, morbidity and development in 463 low birth weight infants fed human milk or formula. However, the feeding groups were not randomly allocated.
Putet 1984	Although not clearly stated in the title or abstract, feeds do not appear to have been randomly assigned.
Svenningsen 1982	Svenningsen 1982 randomly assigned 48 low birth weight infants to formula milk versus breast milk. However, most infants in the breast milk group received their own mother's expressed milk rather than donor breast milk.

Characteristics of excluded studies (*Continued*)

ANALYSES

Comparison 01. Formula milk versus donor breast milk

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Time to regain birth weight (days from birth)	2	166	Weighted Mean Difference (Fixed) 95% CI	-2.00 [-5.81, -2.18]
02 Short term weight change (g/kg/day)	7	649	Weighted Mean Difference (Fixed) 95% CI	2.59 [1.99, 3.20]
03 Short term change in crown-heel length (mm/week)	6	441	Weighted Mean Difference (Fixed) 95% CI	1.14 [0.61, 1.67]
04 Short term change in crown-rump length (mm/week)	1	106	Weighted Mean Difference (Fixed) 95% CI	0.59 [0.08, 1.10]
05 Short term change in femoral length (mm/week)	1	106	Weighted Mean Difference (Fixed) 95% CI	0.34 [0.13, 0.55]
06 Short term change in head circumference (mm/week)	6	515	Weighted Mean Difference (Fixed) 95% CI	1.25 [0.75, 1.75]
07 Weight (kg) at 9 months post term	2	369	Weighted Mean Difference (Fixed) 95% CI	-0.03 [-0.26, 0.21]
08 Length (cm) at 9 months post term	2	369	Weighted Mean Difference (Fixed) 95% CI	0.03 [-0.64, 0.70]
09 Head circumference (cm) at 9 months post term	2	369	Weighted Mean Difference (Fixed) 95% CI	0.20 [-0.13, 0.53]
10 Weight (kg) at 18 months post term	2	438	Weighted Mean Difference (Fixed) 95% CI	0.10 [-0.15, 0.35]
11 Length (cm) at 18 months post term	2	438	Weighted Mean Difference (Fixed) 95% CI	0.53 [-0.15, 1.20]
12 Head circumference (cm) at 18 months post term	2	438	Weighted Mean Difference (Fixed) 95% CI	0.10 [-0.19, 0.39]
13 Weight (kg) at 7.5-8 years of age	2	420	Weighted Mean Difference (Fixed) 95% CI	-0.56 [-1.42, 0.29]
14 Length (cm) at 7.5-8 years of age	2	420	Weighted Mean Difference (Fixed) 95% CI	0.05 [-1.12, 1.23]
15 Head circumference (cm) at 7.5-8 years of age	2	420	Weighted Mean Difference (Fixed) 95% CI	-0.19 [-0.54, 0.16]
16 Bayley mental development index at 18 months	2	387	Weighted Mean Difference (Fixed) 95% CI	1.24 [-2.62, 5.09]
17 Bayley psychomotor development index at 18 months	2	387	Weighted Mean Difference (Fixed) 95% CI	-0.32 [-3.43, 2.79]
18 Neurological impairment at 18 months	2	400	Relative Risk (Fixed) 95% CI	1.21 [0.62, 2.35]
19 Mortality	3	668	Relative Risk (Fixed) 95% CI	1.23 [0.72, 2.11]
20 Necrotising enterocolitis	5	816	Relative Risk (Fixed) 95% CI	2.46 [1.19, 5.08]
21 Suspected necrotising enterocolitis	3	583	Relative Risk (Fixed) 95% CI	1.41 [0.73, 2.71]
22 Feed intolerance or diarrhoea	2	148	Relative Risk (Fixed) 95% CI	4.92 [1.17, 20.70]
23 Incidence of invasive infection	1	166	Relative Risk (Fixed) 95% CI	0.98 [0.66, 1.44]

Comparison 02. Term formula versus donor breast milk

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Short term weight change (g/kg/day)	3	234	Weighted Mean Difference (Fixed) 95% CI	1.74 [0.96, 2.53]
02 Short term change in crown-heel length (mm/week)	2	128	Weighted Mean Difference (Fixed) 95% CI	0.80 [0.10, 1.50]
03 Short term change in head circumference (mm/week)	2	128	Weighted Mean Difference (Fixed) 95% CI	0.81 [0.15, 1.47]
04 Necrotising enterocolitis	1	67	Relative Risk (Fixed) 95% CI	4.73 [0.52, 43.09]
05 Feed intolerance or diarrhoea	1	67	Relative Risk (Fixed) 95% CI	9.46 [1.21, 74.17]

Comparison 03. Preterm formula versus donor breast milk

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Short term weight change (g/kg/day)	4	415	Weighted Mean Difference (Fixed) 95% CI	3.83 [2.88, 4.78]
02 Short term change in crown-heel length (mm/week)	4	313	Weighted Mean Difference (Fixed) 95% CI	1.61 [0.79, 2.42]
03 Short term change in head circumference (mm/week)	4	387	Weighted Mean Difference (Fixed) 95% CI	1.84 [1.07, 2.61]
04 Necrotising enterocolitis	4	749	Relative Risk (Fixed) 95% CI	2.26 [1.04, 4.90]
05 Feed intolerance or diarrhoea	1	81	Relative Risk (Fixed) 95% CI	1.68 [0.16, 17.82]

Comparison 04. Formula milk given as a sole diet versus donor breast milk given as a sole diet

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Short term weight change (g/kg/day)	5	368	Weighted Mean Difference (Fixed) 95% CI	2.68 [1.96, 3.41]
02 Short term change in crown-heel length (mm/week)	4	230	Weighted Mean Difference (Fixed) 95% CI	1.28 [0.66, 1.90]
03 Short term change in head circumference (mm/week)	4	252	Weighted Mean Difference (Fixed) 95% CI	1.45 [0.88, 2.02]
04 Necrotising enterocolitis	3	307	Relative Risk (Fixed) 95% CI	4.05 [1.02, 16.18]

Comparison 05. Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Short term weight change (g/kg/day)	2	281	Weighted Mean Difference (Fixed) 95% CI	2.39 [1.28, 3.50]
02 Short term change in crown-heel length (mm/week)	2	211	Weighted Mean Difference (Fixed) 95% CI	0.75 [-0.28, 1.78]
03 Short term change in head circumference (mm/week)	2	263	Weighted Mean Difference (Fixed) 95% CI	0.59 [-0.44, 1.62]
04 Mortality	2	509	Relative Risk (Fixed) 95% CI	1.16 [0.60, 2.24]
05 Necrotising enterocolitis	2	509	Relative Risk (Fixed) 95% CI	1.96 [0.82, 4.67]
06 Suspected necrotising enterocolitis	1	343	Relative Risk (Fixed) 95% CI	1.07 [0.49, 2.36]

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Low Birth Weight; Infant, Newborn; *Infant, Premature; *Infant Food; Infant Nutrition Physiology; *Milk, Human; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title	Formula milk versus donor breast milk for feeding preterm or low birth weight infants
Authors	Quigley MA, Henderson G, Anthony MY, McGuire W
Contribution of author(s)	William McGuire (WM) and Mary Anthony developed the protocol and undertook the original review in 2000. Ginny Henderson and WM updated the review in 2003. Maria Quigley and WM revised the protocol and updated the review in 2007.
Issue protocol first published	2001/1
Review first published	2001/4
Date of most recent amendment	22 August 2007
Date of most recent SUBSTANTIVE amendment	18 June 2007
What's New	<p>This updates the review "Formula milk versus term human milk for feeding preterm or low birth weight infants" published in The Cochrane Library, Issue 1, 2004 (Henderson 2004). In this update, the structure of the review has been revised in the following manner:</p> <ol style="list-style-type: none">1. Trials that compared feeding with formula milk with either term or preterm donor breast milk (previous review restricted to term breast milk).2. Trials that compared feeding with formula versus donor breast milk as a sole diet or as a supplement to maternal expressed breast milk (previous review restricted to sole diet). <p>This update includes one trial published since the previous update (Schlanler 2005), and one older trial that was not included in the previous review (Lucas 1984b). The major change to the review findings is that the meta-analysis now detects a statistically significantly higher rate of necrotising enterocolitis in the formula fed group.</p>
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI 10.1002/14651858.CD002971.pub2
Cochrane Library number CD002971
Editorial group Cochrane Neonatal Group
Editorial group code HM-NEONATAL

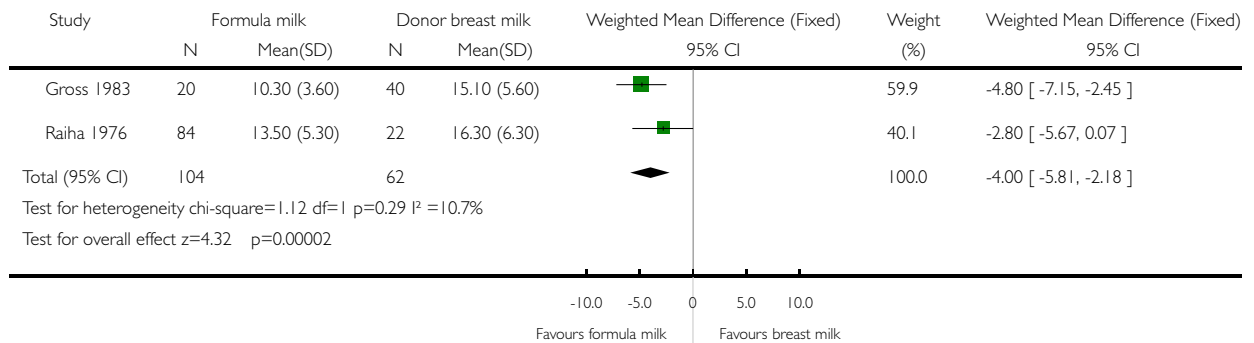
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Formula milk versus donor breast milk, Outcome 01 Time to regain birth weight (days from birth)

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 01 Time to regain birth weight (days from birth)

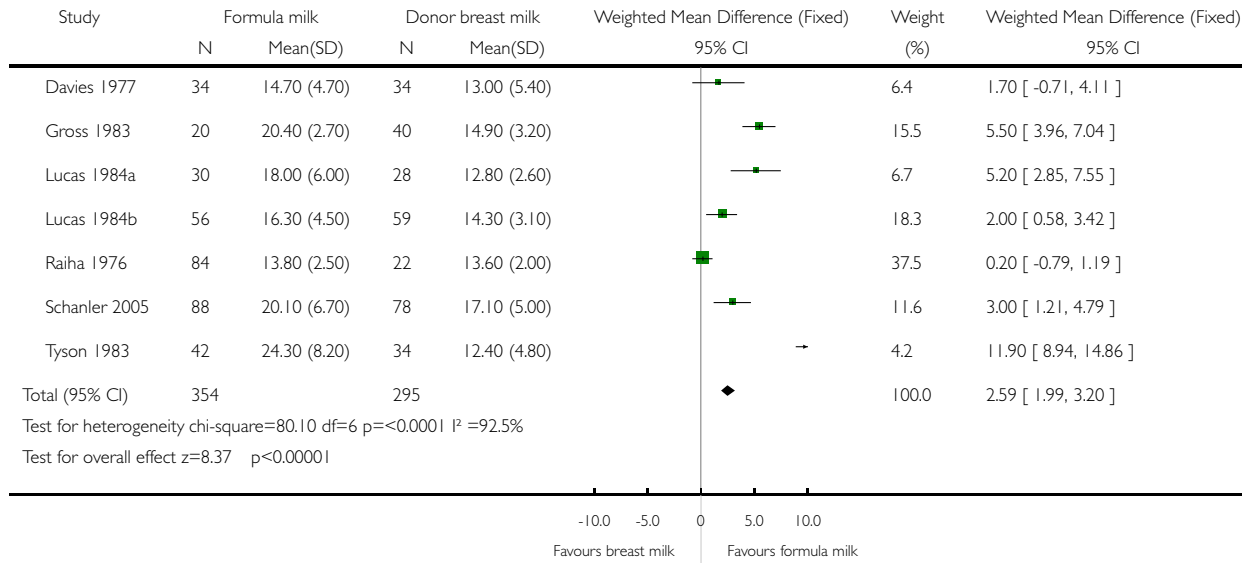


Analysis 01.02. Comparison 01 Formula milk versus donor breast milk, Outcome 02 Short term weight change (g/kg/day)

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 02 Short term weight change (g/kg/day)

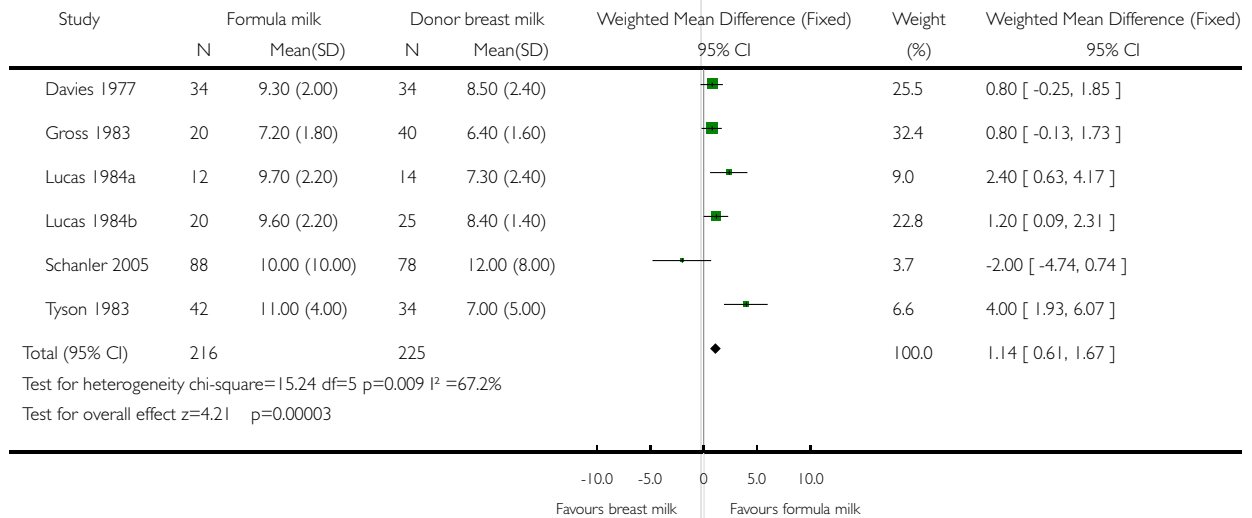


Analysis 01.03. Comparison 01 Formula milk versus donor breast milk, Outcome 03 Short term change in crown-heel length (mm/week)

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 03 Short term change in crown-heel length (mm/week)

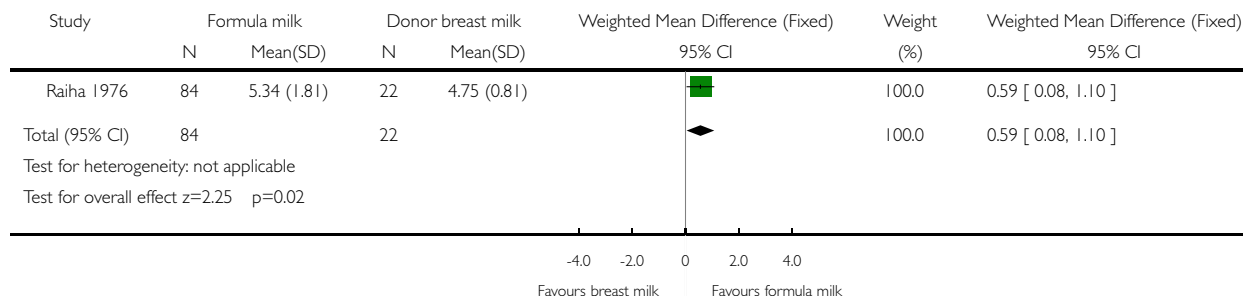


Analysis 01.04. Comparison 01 Formula milk versus donor breast milk, Outcome 04 Short term change in crown-rump length (mm/week)

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 04 Short term change in crown-rump length (mm/week)

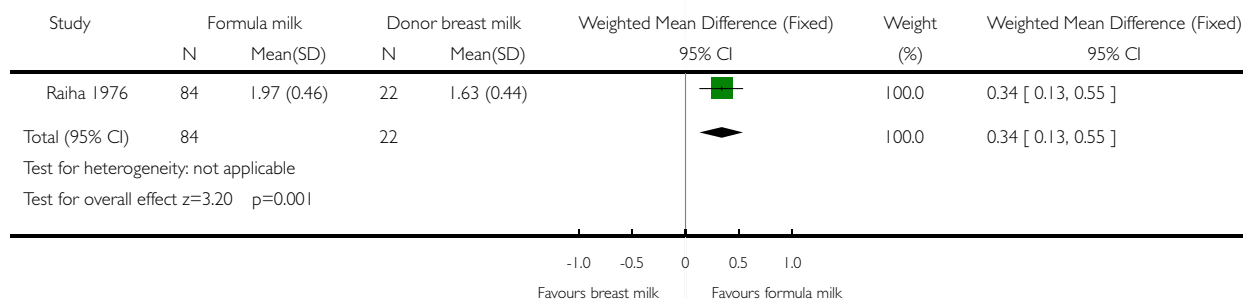


Analysis 01.05. Comparison 01 Formula milk versus donor breast milk, Outcome 05 Short term change in femoral length (mm/week)

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 05 Short term change in femoral length (mm/week)

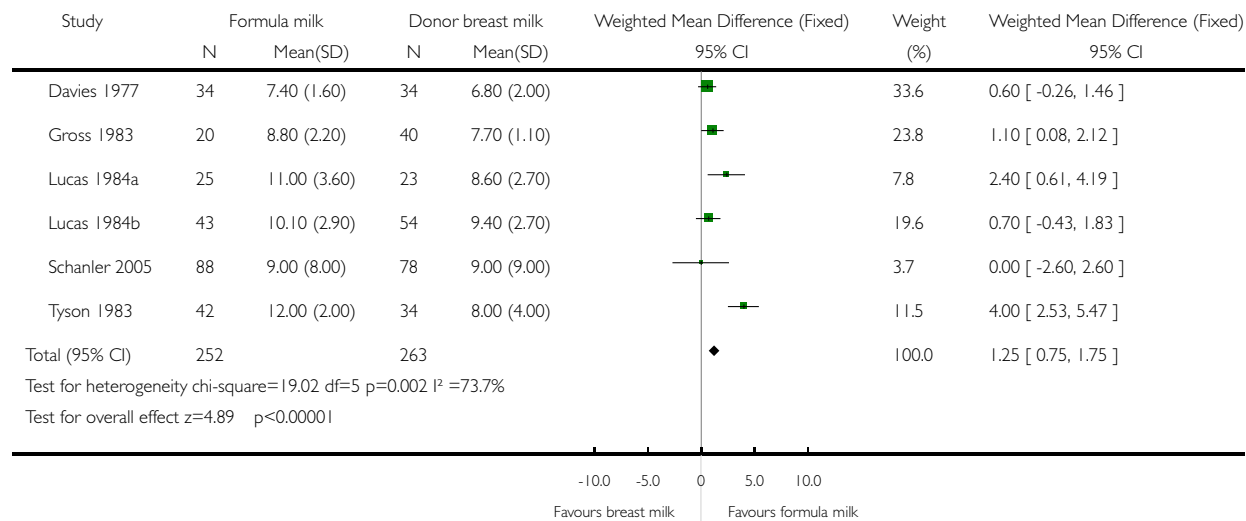


Analysis 01.06. Comparison 01 Formula milk versus donor breast milk, Outcome 06 Short term change in head circumference (mm/week)

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Comparison: 01 Formula milk versus donor breast milk

Outcome: 06 Short term change in head circumference (mm/week)

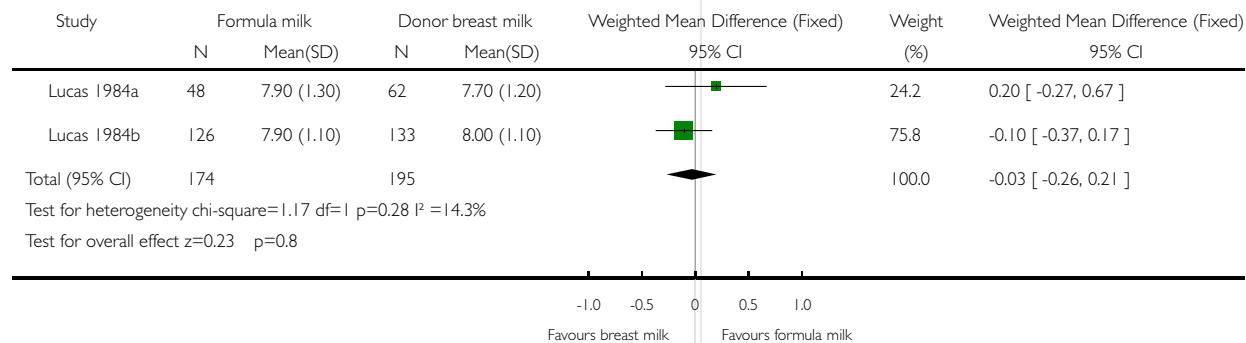


Analysis 01.07. Comparison 01 Formula milk versus donor breast milk, Outcome 07 Weight (kg) at 9 months post term

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 07 Weight (kg) at 9 months post term

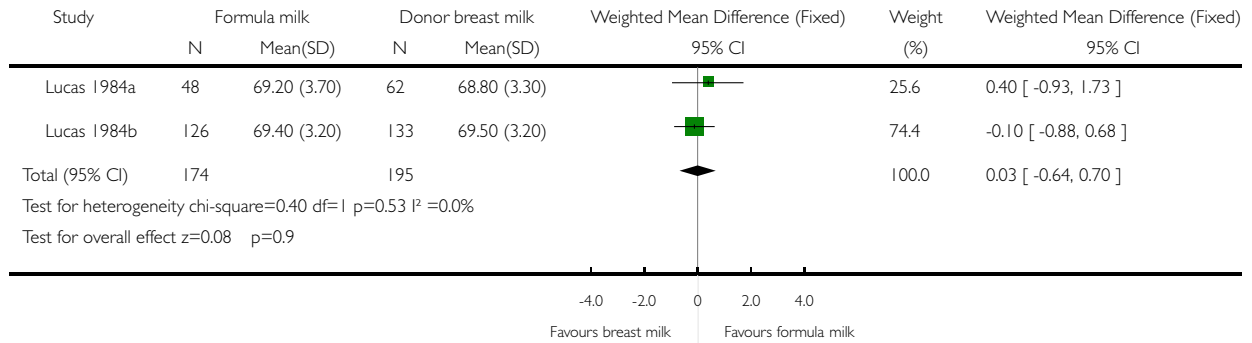


Analysis 01.08. Comparison 01 Formula milk versus donor breast milk, Outcome 08 Length (cm) at 9 months post term

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 08 Length (cm) at 9 months post term

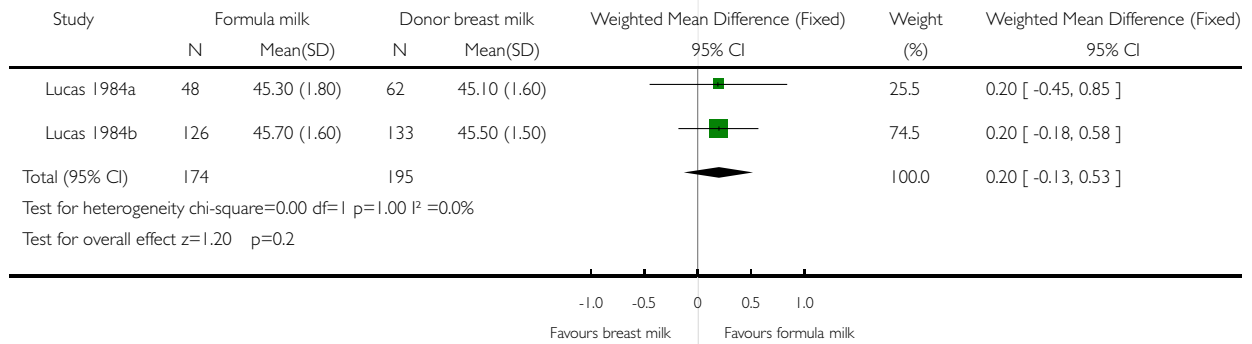


Analysis 01.09. Comparison 01 Formula milk versus donor breast milk, Outcome 09 Head circumference (cm) at 9 months post term

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 09 Head circumference (cm) at 9 months post term



Analysis 01.10. Comparison 01 Formula milk versus donor breast milk, Outcome 10 Weight (kg) at 18 months post term

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 10 Weight (kg) at 18 months post term

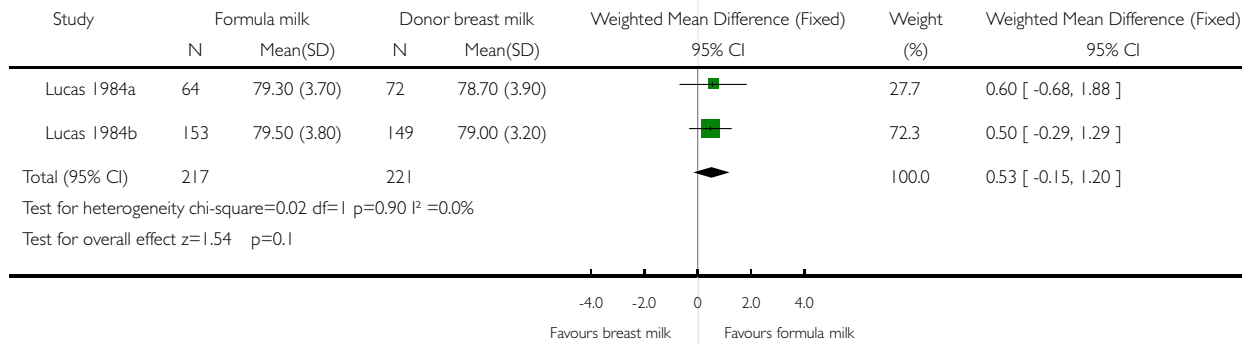


Analysis 01.11. Comparison 01 Formula milk versus donor breast milk, Outcome 11 Length (cm) at 18 months post term

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 11 Length (cm) at 18 months post term

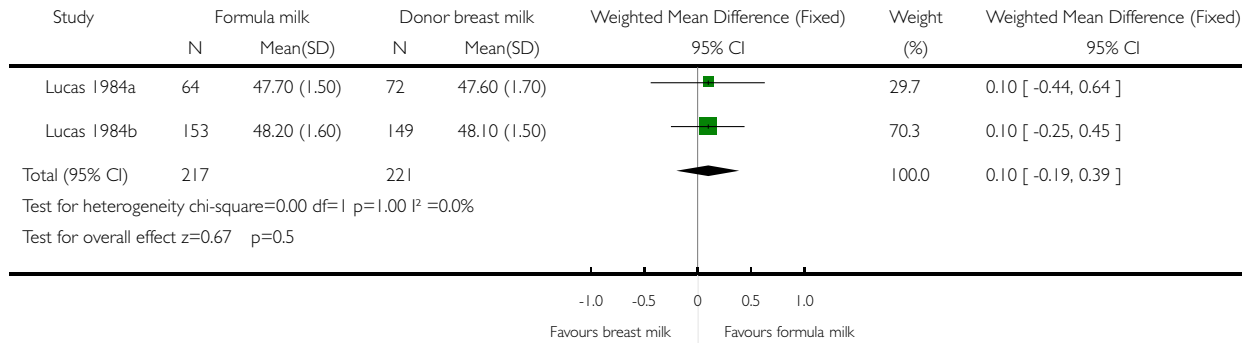


Analysis 01.12. Comparison 01 Formula milk versus donor breast milk, Outcome 12 Head circumference (cm) at 18 months post term

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 12 Head circumference (cm) at 18 months post term

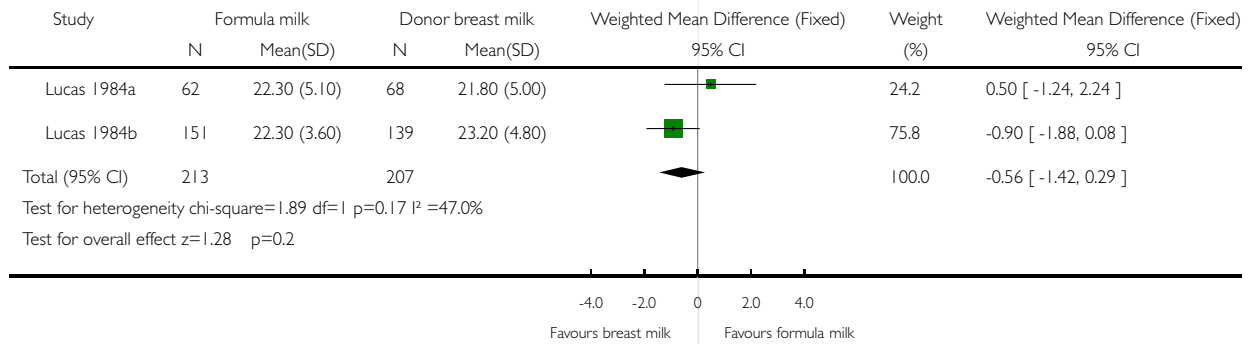


Analysis 01.13. Comparison 01 Formula milk versus donor breast milk, Outcome 13 Weight (kg) at 7.5-8 years of age

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 13 Weight (kg) at 7.5-8 years of age

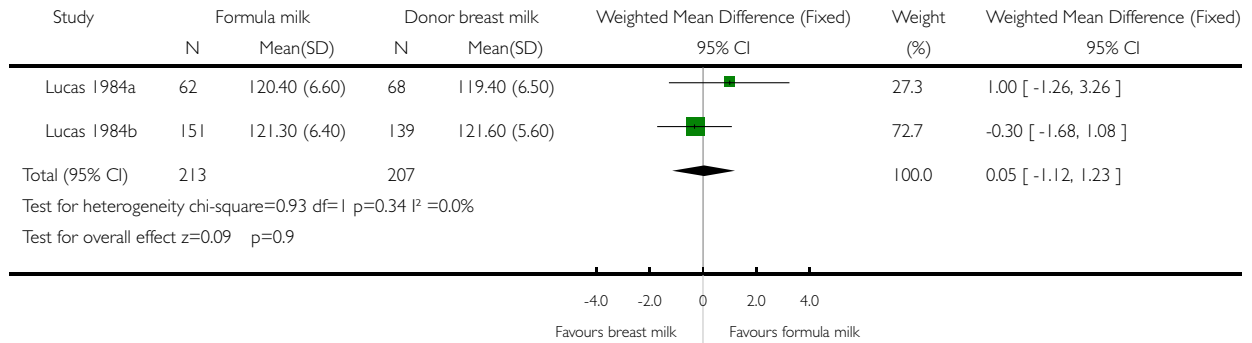


Analysis 01.14. Comparison 01 Formula milk versus donor breast milk, Outcome 14 Length (cm) at 7.5-8 years of age

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 14 Length (cm) at 7.5-8 years of age

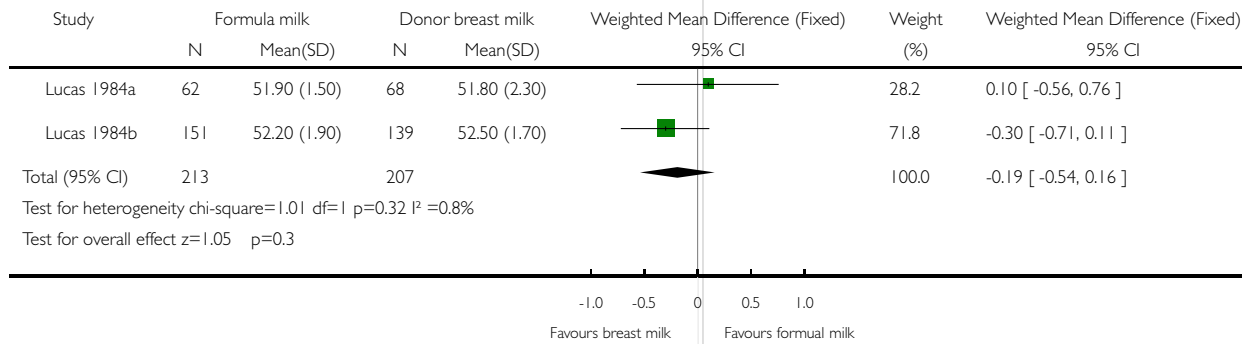


Analysis 01.15. Comparison 01 Formula milk versus donor breast milk, Outcome 15 Head circumference (cm) at 7.5-8 years of age

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 15 Head circumference (cm) at 7.5-8 years of age

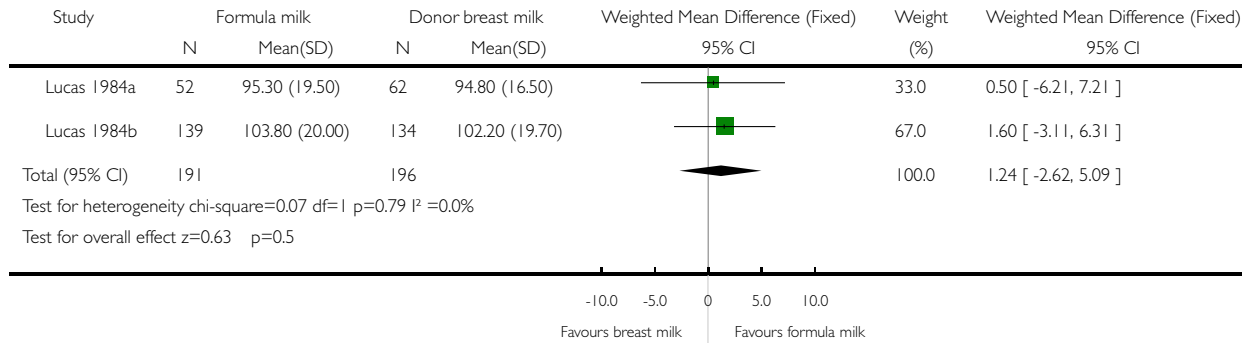


Analysis 01.16. Comparison 01 Formula milk versus donor breast milk, Outcome 16 Bayley mental development index at 18 months

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 16 Bayley mental development index at 18 months

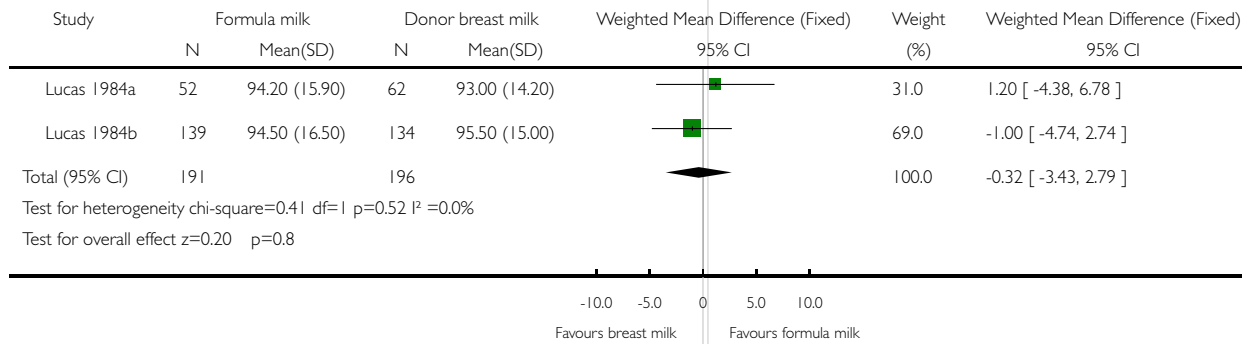


Analysis 01.17. Comparison 01 Formula milk versus donor breast milk, Outcome 17 Bayley psychomotor development index at 18 months

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 17 Bayley psychomotor development index at 18 months

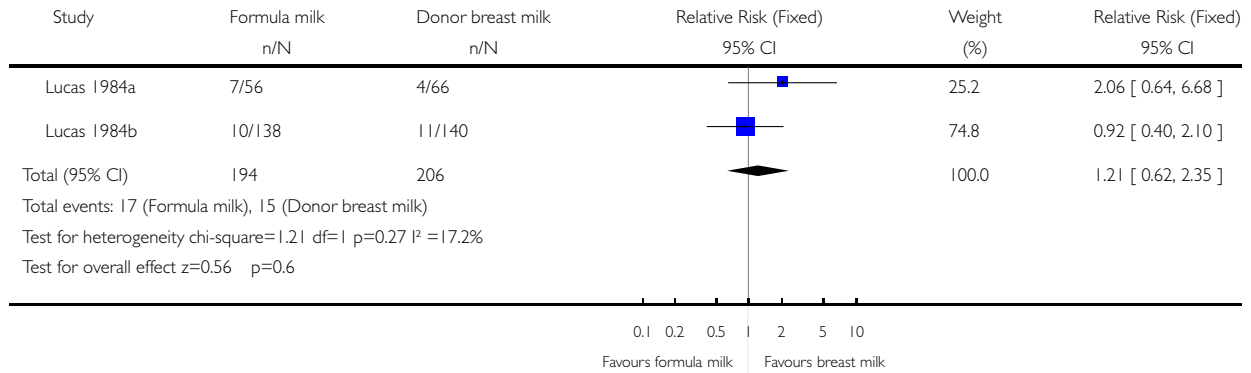


Analysis 01.18. Comparison 01 Formula milk versus donor breast milk, Outcome 18 Neurological impairment at 18 months

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 18 Neurological impairment at 18 months

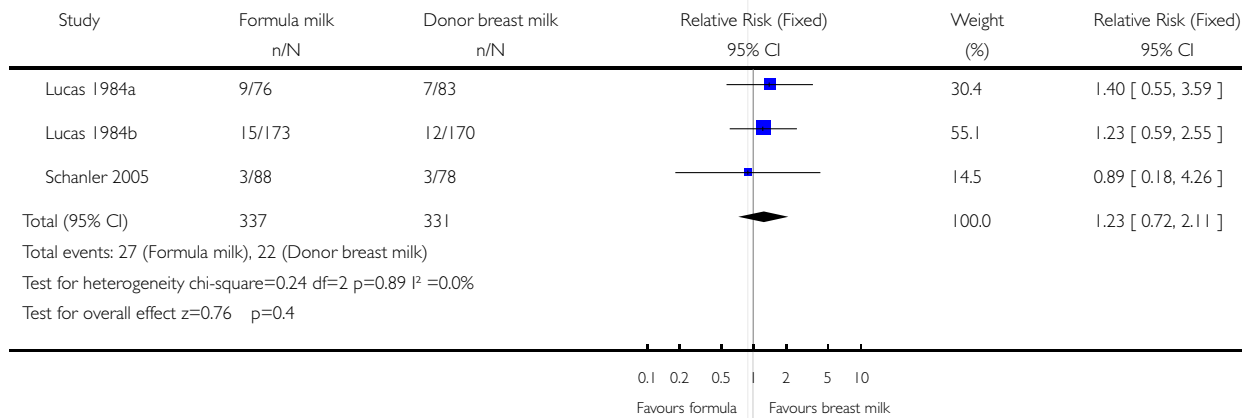


Analysis 01.19. Comparison 01 Formula milk versus donor breast milk, Outcome 19 Mortality

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 19 Mortality

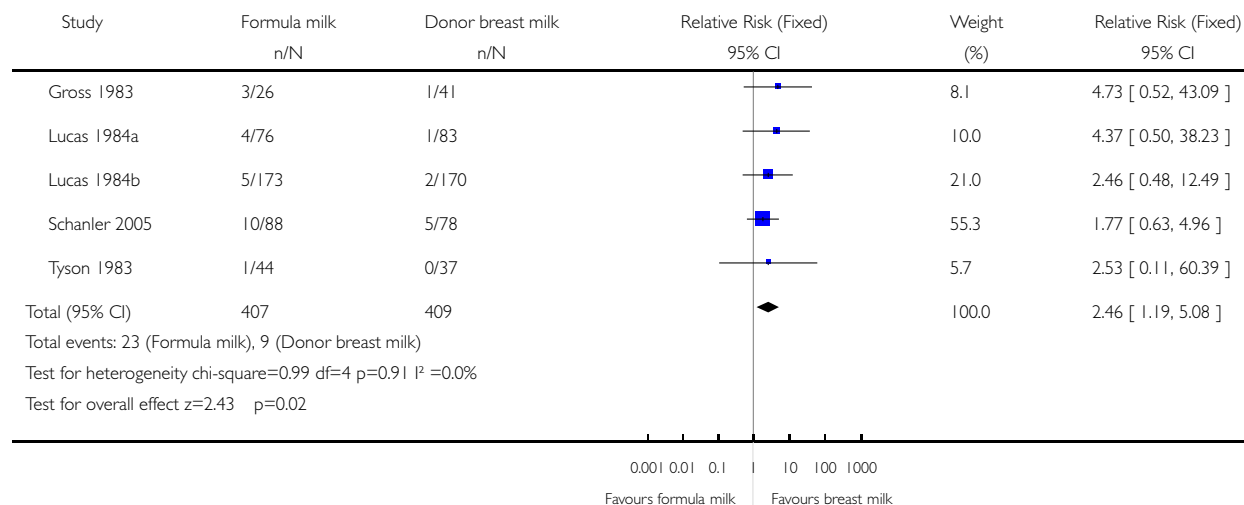


Analysis 01.20. Comparison 01 Formula milk versus donor breast milk, Outcome 20 Necrotising enterocolitis

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 20 Necrotising enterocolitis

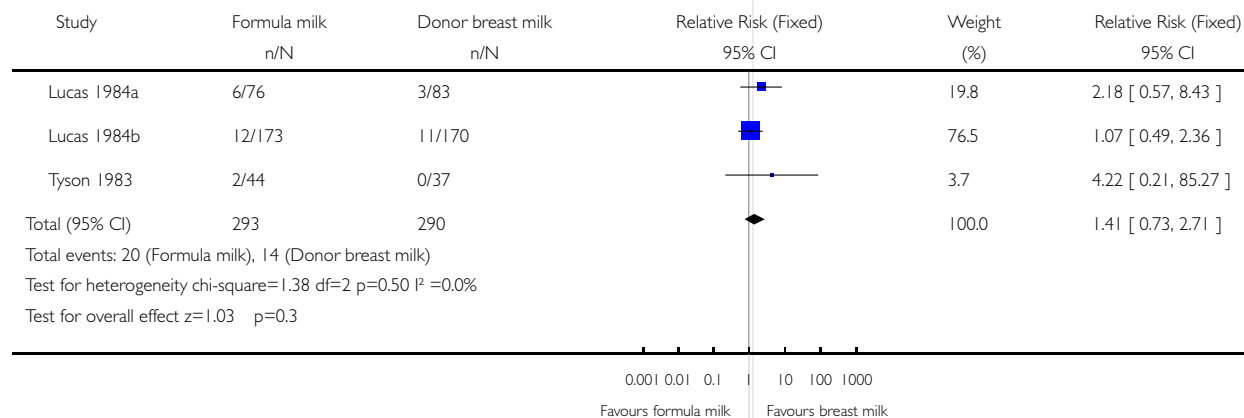


Analysis 01.21. Comparison 01 Formula milk versus donor breast milk, Outcome 21 Suspected necrotising enterocolitis

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 21 Suspected necrotising enterocolitis

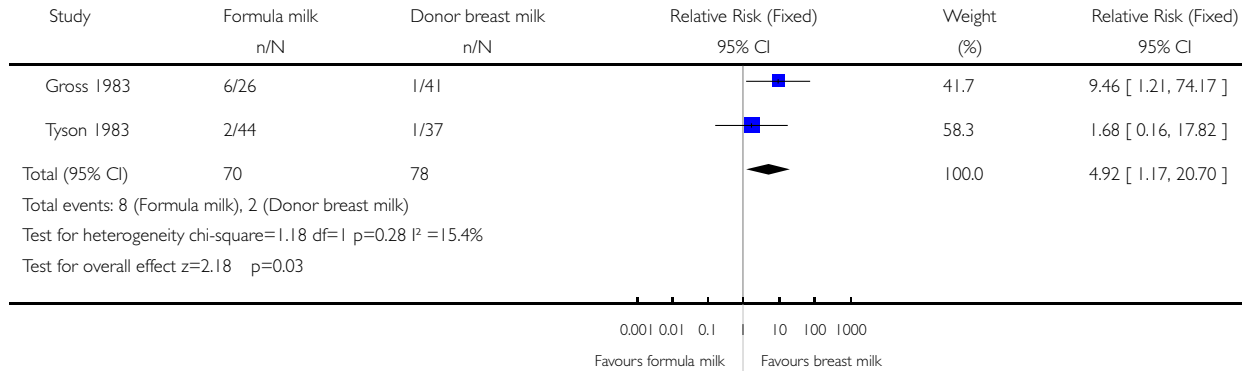


Analysis 01.22. Comparison 01 Formula milk versus donor breast milk, Outcome 22 Feed intolerance or diarrhoea

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 22 Feed intolerance or diarrhoea

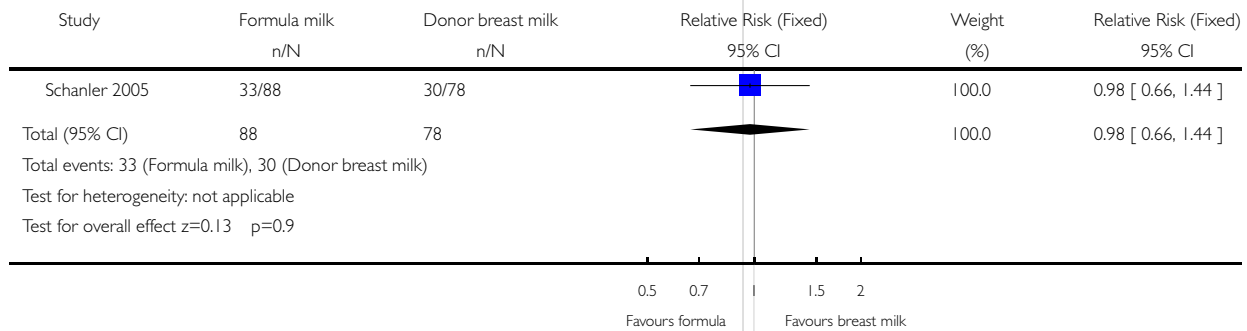


Analysis 01.23. Comparison 01 Formula milk versus donor breast milk, Outcome 23 Incidence of invasive infection

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

Comparison: 01 Formula milk versus donor breast milk

Outcome: 23 Incidence of invasive infection

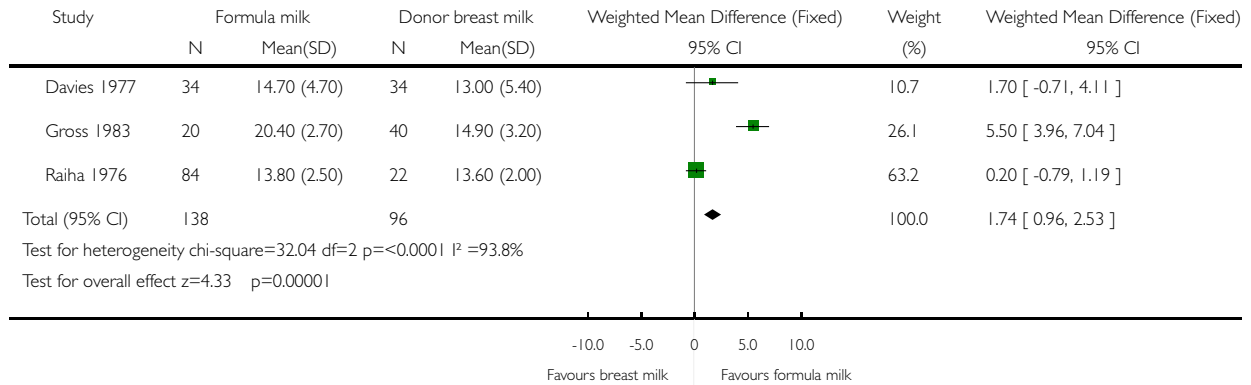


Analysis 02.01. Comparison 02 Term formula versus donor breast milk, Outcome 01 Short term weight change (g/kg/day)

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

Comparison: 02 Term formula versus donor breast milk

Outcome: 01 Short term weight change (g/kg/day)

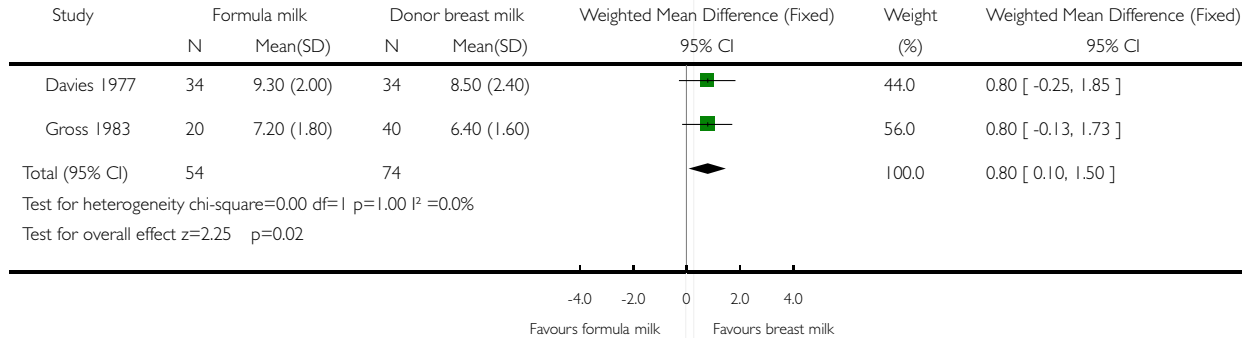


Analysis 02.02. Comparison 02 Term formula versus donor breast milk, Outcome 02 Short term change in crown-heel length (mm/week)

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

Comparison: 02 Term formula versus donor breast milk

Outcome: 02 Short term change in crown-heel length (mm/week)

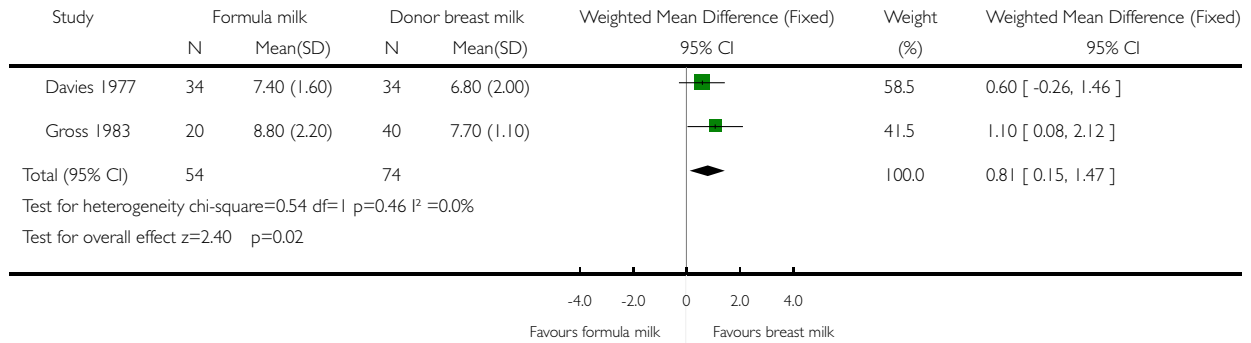


Analysis 02.03. Comparison 02 Term formula versus donor breast milk, Outcome 03 Short term change in head circumference (mm/week)

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

Comparison: 02 Term formula versus donor breast milk

Outcome: 03 Short term change in head circumference (mm/week)

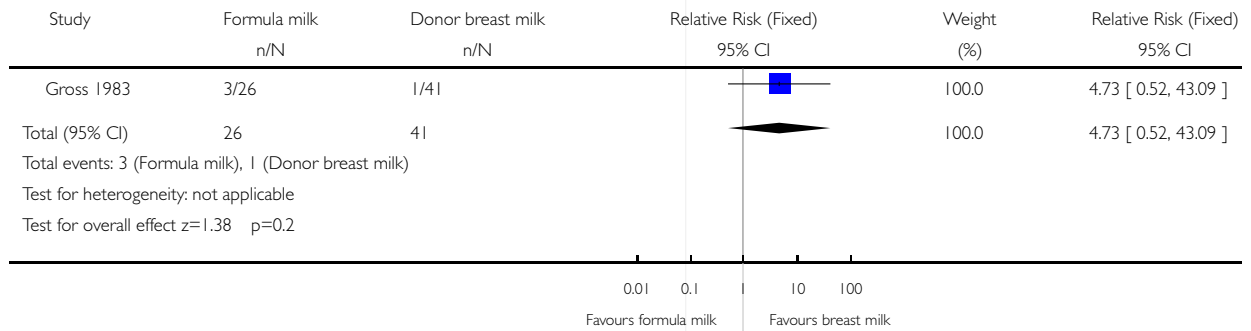


Analysis 02.04. Comparison 02 Term formula versus donor breast milk, Outcome 04 Necrotising enterocolitis

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

Comparison: 02 Term formula versus donor breast milk

Outcome: 04 Necrotising enterocolitis

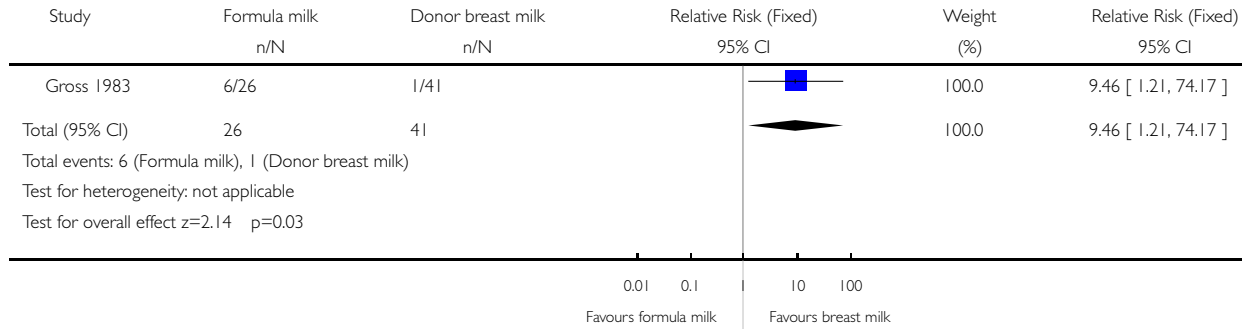


Analysis 02.05. Comparison 02 Term formula versus donor breast milk, Outcome 05 Feed intolerance or diarrhoea

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

Comparison: 02 Term formula versus donor breast milk

Outcome: 05 Feed intolerance or diarrhoea

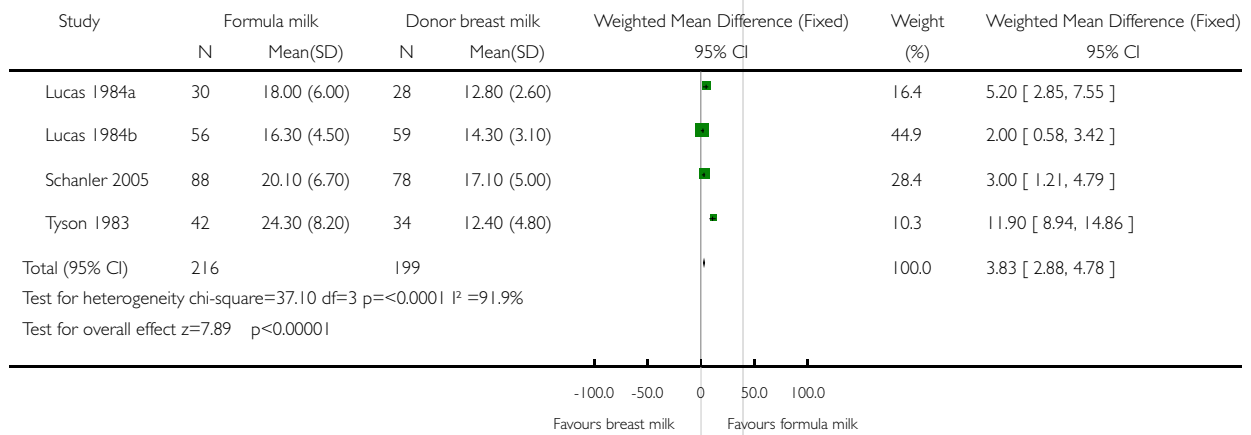


Analysis 03.01. Comparison 03 Preterm formula versus donor breast milk, Outcome 01 Short term weight change (g/kg/day)

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

Comparison: 03 Preterm formula versus donor breast milk

Outcome: 01 Short term weight change (g/kg/day)

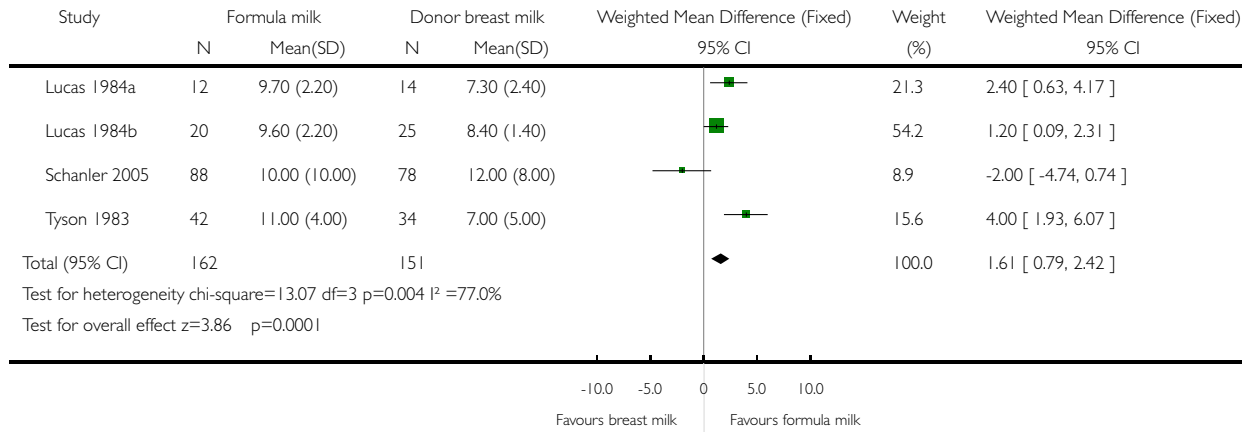


Analysis 03.02. Comparison 03 Preterm formula versus donor breast milk, Outcome 02 Short term change in crown-heel length (mm/week)

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

Comparison: 03 Preterm formula versus donor breast milk

Outcome: 02 Short term change in crown-heel length (mm/week)

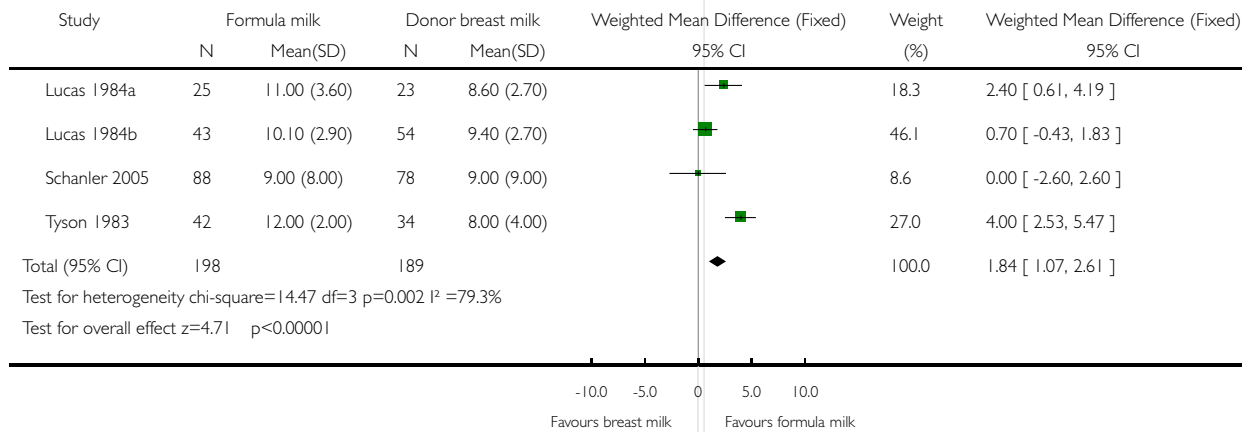


Analysis 03.03. Comparison 03 Preterm formula versus donor breast milk, Outcome 03 Short term change in head circumference (mm/week)

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

Comparison: 03 Preterm formula versus donor breast milk

Outcome: 03 Short term change in head circumference (mm/week)

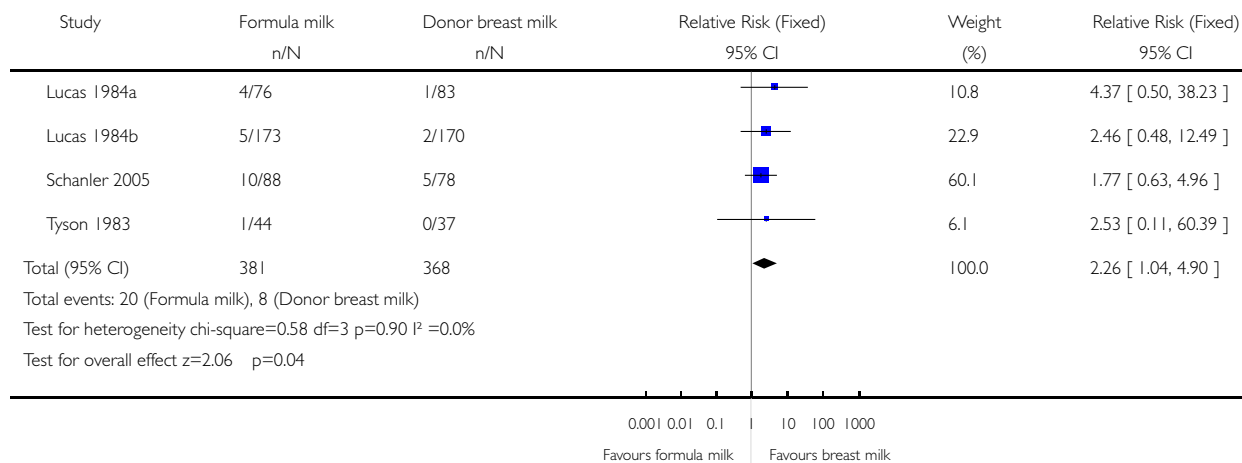


Analysis 03.04. Comparison 03 Preterm formula versus donor breast milk, Outcome 04 Necrotising enterocolitis

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

Comparison: 03 Preterm formula versus donor breast milk

Outcome: 04 Necrotising enterocolitis

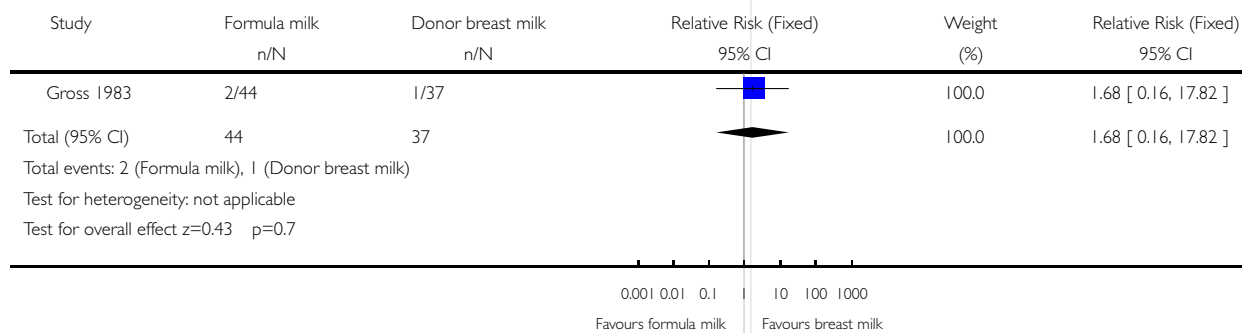


Analysis 03.05. Comparison 03 Preterm formula versus donor breast milk, Outcome 05 Feed intolerance or diarrhoea

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

Comparison: 03 Preterm formula versus donor breast milk

Outcome: 05 Feed intolerance or diarrhoea

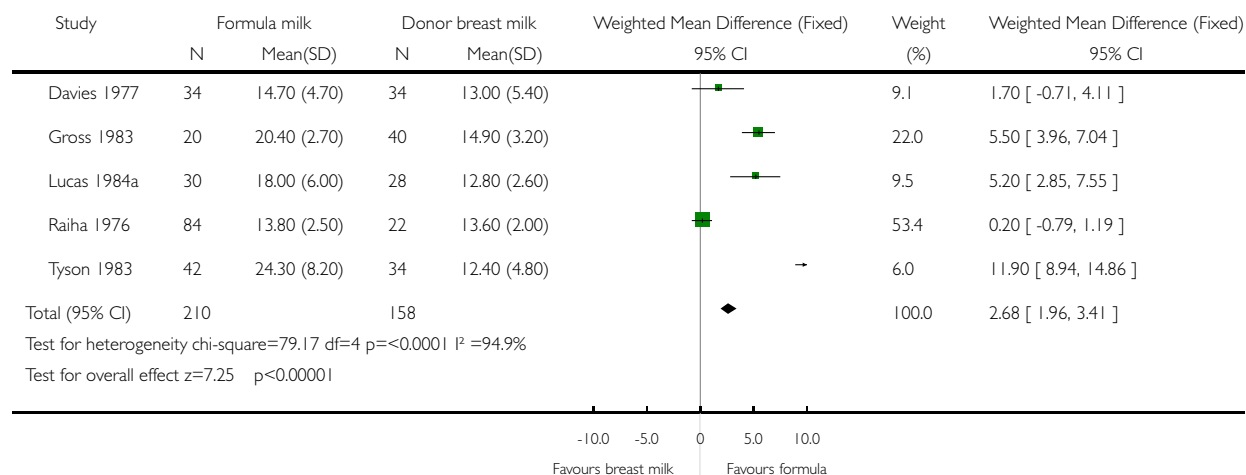


Analysis 04.01. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 01 Short term weight change (g/kg/day)

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

Comparison: 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet

Outcome: 01 Short term weight change (g/kg/day)

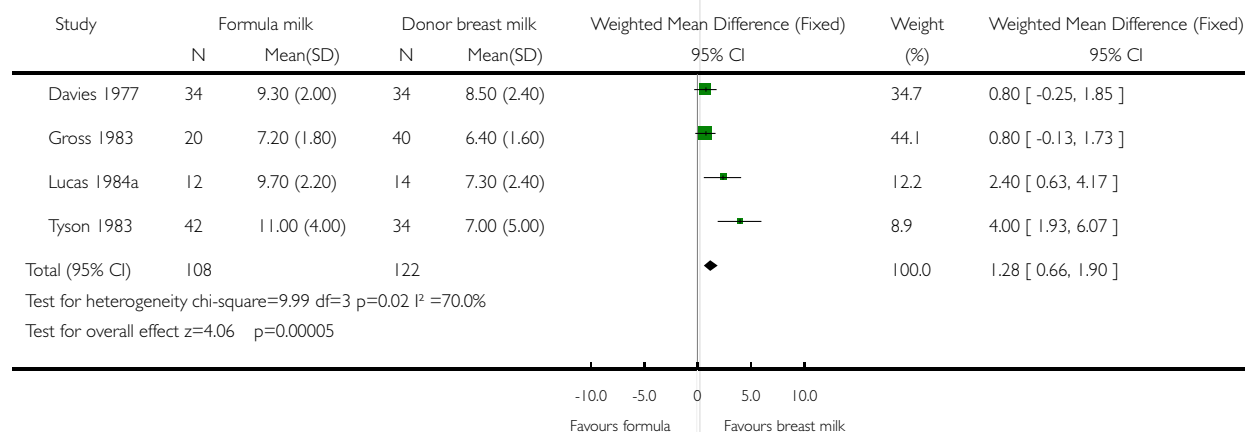


Analysis 04.02. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 02 Short term change in crown-heel length (mm/week)

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

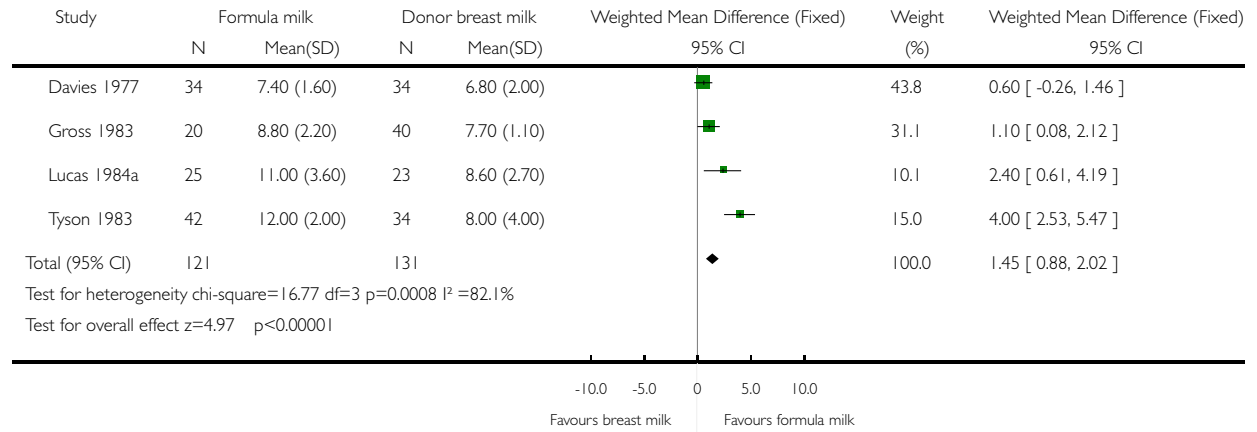
Comparison: 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet

Outcome: 02 Short term change in crown-heel length (mm/week)



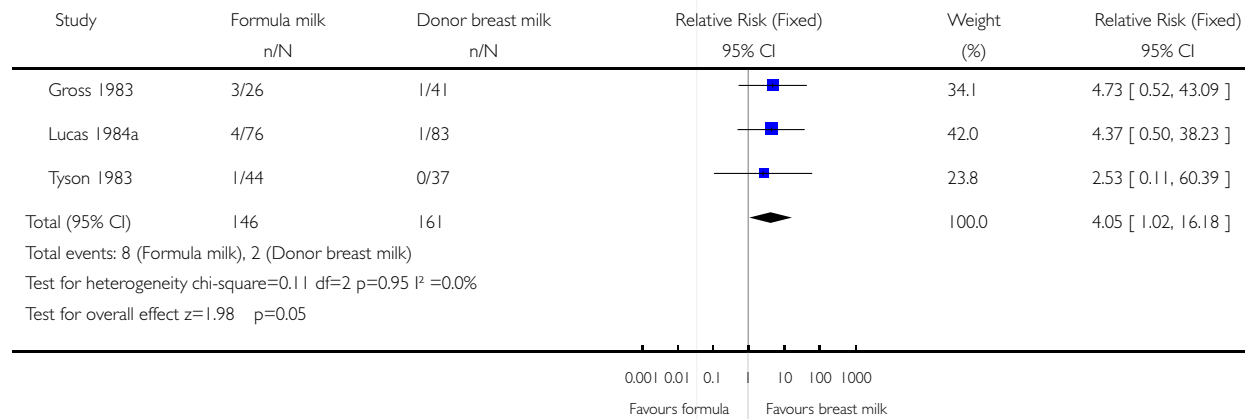
Analysis 04.03. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 03 Short term change in head circumference (mm/week)

Review: Formula milk versus donor breast milk for feeding preterm or low birth weight infants
 Comparison: 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet
 Outcome: 03 Short term change in head circumference (mm/week)



Analysis 04.04. Comparison 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet, Outcome 04 Necrotising enterocolitis

Review: Formula milk versus donor breast milk for feeding preterm or low birth weight infants
 Comparison: 04 Formula milk given as a sole diet versus donor breast milk given as a sole diet
 Outcome: 04 Necrotising enterocolitis

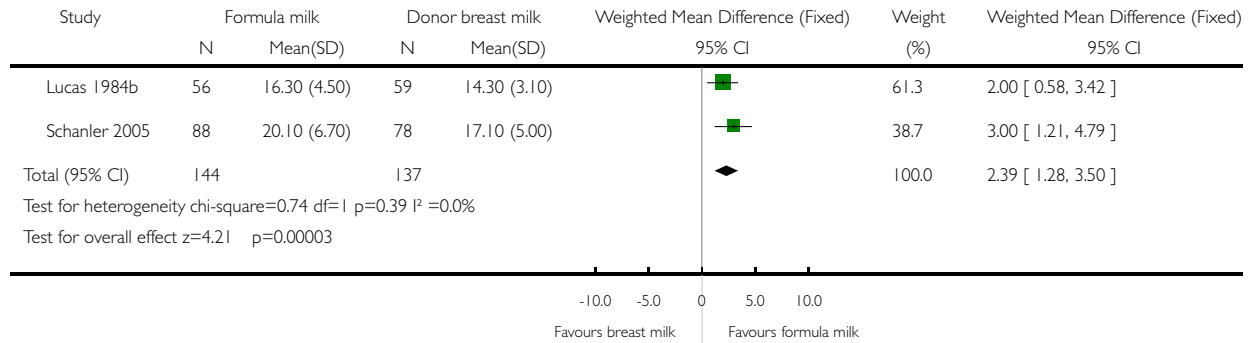


Analysis 05.01. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 01 Short term weight change (g/kg/day)

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

Comparison: 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome: 01 Short term weight change (g/kg/day)

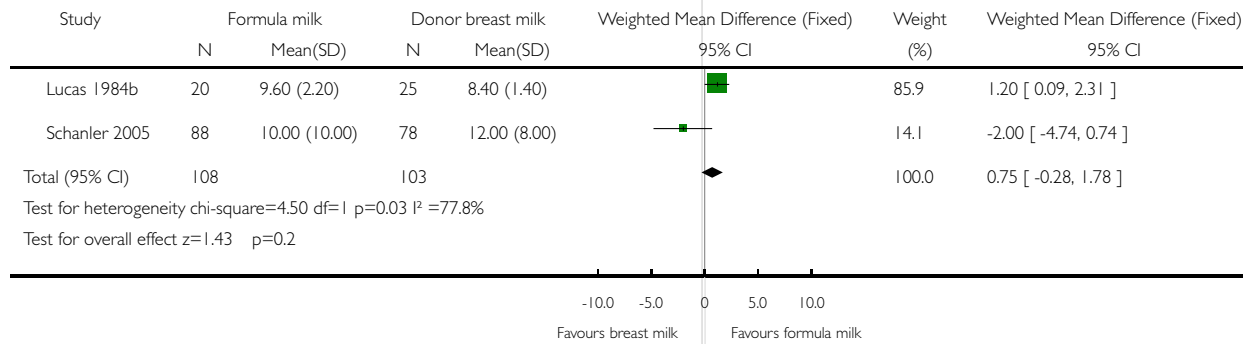


Analysis 05.02. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 02 Short term change in crown-heel length (mm/week)

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

Comparison: 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome: 02 Short term change in crown-heel length (mm/week)

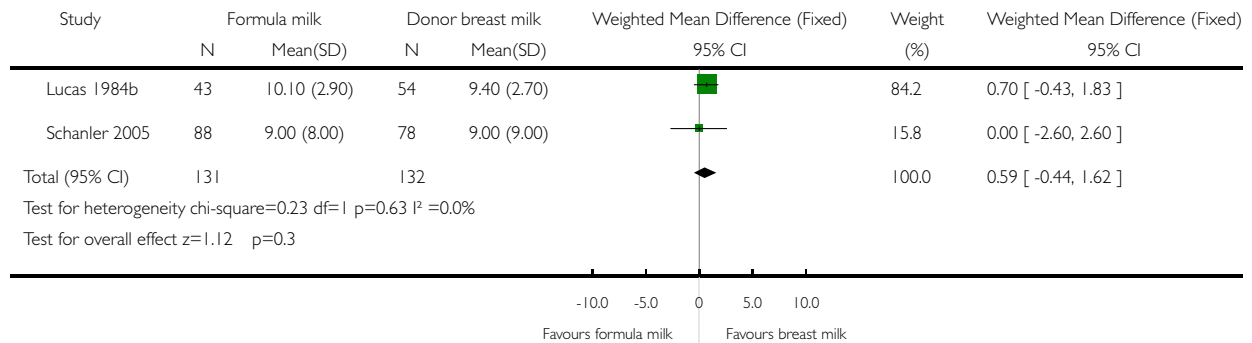


Analysis 05.03. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 03 Short term change in head circumference (mm/week)

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

Comparison: 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome: 03 Short term change in head circumference (mm/week)

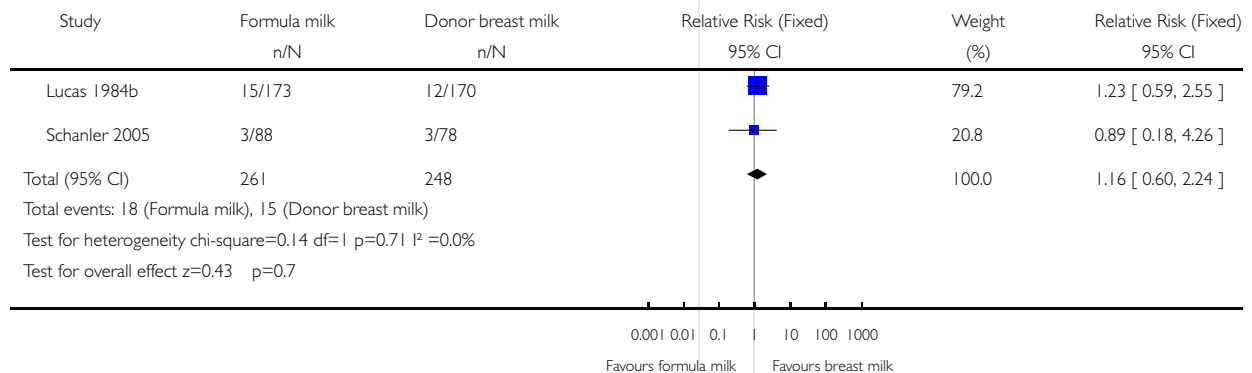


Analysis 05.04. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 04 Mortality

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

Comparison: 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome: 04 Mortality

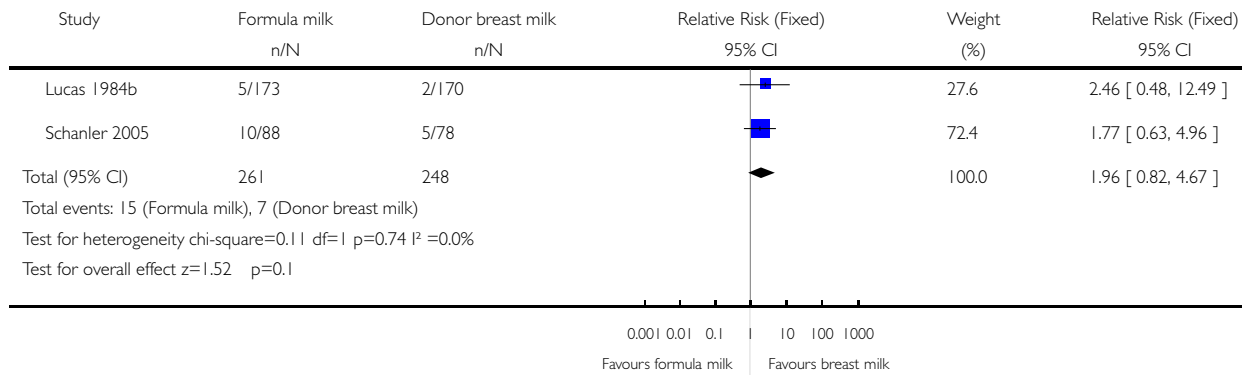


Analysis 05.05. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 05 Necrotising enterocolitis

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

Comparison: 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome: 05 Necrotising enterocolitis



Analysis 05.06. Comparison 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk, Outcome 06 Suspected necrotising enterocolitis

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

Comparison: 05 Formula milk versus donor breast milk given as a supplement to maternal breast milk

Outcome: 06 Suspected necrotising enterocolitis

