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TABLE OF CONTENTS

[Intervention Review]

Multi-nutrient fortification of human milk for preterm infants

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ABSTRACT

Background

Exclusively breast milk-fed preterm infants may accumulate nutrient deficits leading to extrauterine growth restriction. Feeding preterm infants with multi-nutrient fortified human breast milk rather than unfortified breast milk may increase nutrient accretion and growth rates and may improve neurodevelopmental outcomes.

Objectives

To determine whether multi-nutrient fortified human breast milk improves important outcomes (including growth and development) over unfortified breast milk for preterm infants without increasing the risk of adverse effects (such as feed intolerance and necrotising enterocolitis).

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2), MEDLINE, EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (until February 2016), as well as conference proceedings and previous reviews.

Selection criteria

Randomised and quasi-randomised controlled trials that compared feeding preterm infants with multi-nutrient (protein and energy plus minerals, vitamins or other nutrients) fortified human breast milk versus unfortified (no added protein or energy) breast milk.

Data collection and analysis

We extracted data using the standard methods of the Cochrane Neonatal Review Group. We separately evaluated trial quality, data extracted by two review authors and data synthesised using risk ratios (RRs), risk differences and mean differences (MDs). We assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We identified 14 trials in which a total of 1071 infants participated. The trials were generally small and weak methodologically. Meta-analyses provided low-quality evidence that multi-nutrient fortification of breast milk increases in-hospital rates of growth (MD 1.81 g/kg/d, 95% confidence interval (CI) 1.23 to 2.40); length (MD 0.12 cm/wk, 95% CI 0.07 to 0.17); and head circumference (MD 0.08 cm/wk, 95% CI 0.04 to 0.12). Only very limited data are available for growth and developmental outcomes assessed beyond infancy, and these show no effects of fortification. The data did not indicate other potential benefits or harms and provided low-quality evidence that fortification does not increase the risk of necrotising enterocolitis in preterm infants (typical RR 1.57, 95% CI 0.76 to 3.23; 11 studies, 882 infants).

Authors' conclusions

Limited available data do not provide strong evidence that feeding preterm infants with multi-nutrient fortified breast milk compared with unfortified breast milk affects important outcomes, except that it leads to slightly increased in-hospital growth rates.

PLAIN LANGUAGE SUMMARY

Multi-nutrient fortification of breast milk for preterm infants

Review question: Does feeding preterm infants with breast milk fortified with extra nutrients (including protein and energy) compared with unfortified breast milk increase growth rate and improve development?

Background: Breast milk alone may not provide preterm infants with sufficient quantities of nutrients to support optimal growth and development. Mutli-nutrient fortifiers (powder or liquid supplements of protein, energy from carbohydrates or fat and other nutrients, usually extracted from cow's milk) can be added to breast milk to increase nutrient content by about 10%. Feeding preterm infants, particularly very preterm infants, with multi-nutrient fortified breast milk may increase nutrient intake and growth rates, and may improve development.

Study characteristics: We found 14 trials; most were small (involving 1071 infants in total) and were flawed methodologically.

Key results: Multi-nutrient fortification of breast milk for preterm infants is associated with small increases in rates of weight gain, length gain and head growth during neonatal unit admission. Only very limited data are available for growth and developmental outcomes assessed beyond infancy, and these show no effects of fortification. Trials report no consistent evidence of other potential benefits or harms of fortification, including effects on risk of feeding or bowel problems.

Conclusions: Although available trial data show that multi-nutrient fortification increases growth rates of preterm infants during their initial hospital admission, they do not provide consistent evidence on effects on longer-term growth or development. Additional trials are needed to resolve this issue.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Patient or population: preterm infants
Setting: healthcare setting
Intervention: fortified breast milk
Comparison: unfortified breast milk

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with unfortified breast milk	Risk with fortified breast milk			
Weight gain (g/kg/d)	Comparator	Mean weight gain was 1.81 g/kg/d more (1.23 more to 2.4 more)	-	635 (10 RCTs)	⊕⊕◯◯ Low[a,b]
Length gain (cm/wk)	Comparator	Mean length gain was 0.12 cm/wk more (0.07 more to 0.17 more)	-	555 (8 RCTs)	⊕⊕◯◯ Low[a,b]
Head growth (cm/wk)	Comparator	Mean head growth was 0.08 cm/wk more (0.04 more to 0.12 more)	-	555 (8 RCTs)	⊕⊕⊕◯ Moderate[b]
Mental development index (MDI) at 18 months	Comparator	Mean MDI was 2.2 more (3.35 fewer to 7.75 more)	-	245 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Psychomotor development index (PDI) at 18 months	Comparator	Mean PDI was 2.4 more (1.9 fewer to 6.7 more)	-	245 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Necrotising enterocolitis	Study population		RR 1.57 (0.76 to 3.23)	882 (11 RCTs)	⊕⊕◯◯ Low[b,d]
	25 per 1000	40 per 1000 (19 to 82)			

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

__CI__ - confidence interval; __RR__ - risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

[a] Unexplained heterogeneity
[b] Uncertainty about methods used to generate random sequence, conceal allocation and blind assessments in most trials
[c] Estimates of effect consistent with both substantial harms and benefits
[d] 95% CI of RR consistent with 3-fold increase in risk with intervention

BACKGROUND

Description of the condition

Most preterm infants accumulate energy, protein, mineral and other nutrient deficits during the initial neonatal unit admission (Embleton 2001; Cooke 2004). By the time they are ready to go home, typically at around 36 to 40 weeks' postmenstrual age, many infants, especially those born very preterm or very low birth weight (VLBW), are substantially growth-restricted relative to their term-born peers (Ehrenkranz 1999; Steward 2002; Clark 2003; Dusick 2003). Although very preterm or VLBW infants usually attain some "catch-up" growth following hospital discharge, growth deficits can persist through childhood and adolescence and into adulthood (Dusick 2003; Euser 2008). Slow postnatal growth is associated with neurodevelopmental impairment in later childhood and with poorer cognitive and educational outcomes (Brandt 2003; Leppanen 2014). Preterm infants who have accumulated mineral deficits have higher risks of metabolic bone disease and slow skeletal growth compared with infants born at term, although uncertainty remains about long-term effects on bone mass and health (Fewtrell 2011). Furthermore, researchers have expressed concern that nutritional deficiency and growth restriction in utero and during early infancy may have consequences for long-term metabolic and cardiovascular health (Embleton 2013; Lapillonne 2013).

Description of the intervention

Multi-nutrient fortification of breast milk

Human breast milk is the recommended form of enteral nutrition for newborn infants for at least the first six months of postnatal life (Johnston 2012). Breast milk alone, however, may not meet the recommended nutritional needs of growing preterm infants (Embleton 2007; Agostoni 2010). International consensus guidelines state that "standard" volumes (about 150 to 180 mL/kg/d) of breast milk do not provide the recommended amount of energy (110 to 135 kcal/kg/d) or protein (3.5 to 4.5 g/kg/d) to meet the metabolic needs of preterm infants (AAP 2004; Agostoni 2010). The strategy most commonly employed in neonatal care facilities in high-income countries to address these potential nutrient deficits is to supplement breast milk with extra nutrients, usually in the form of a powder or liquid "multi-nutrient fortifier" (Gregory 2012; Klingenberg 2012; Cormack 2013; Tudehope 2013; Dutta 2015). Most commercially available multi-nutrient fortifiers are derived from cow's milk, but fortifiers derived from human milk have been developed recently (Rochow 2015).

Fortifiers are intended to be mixed with expressed breast milk with the aim of achieving about 10% nutrient enrichment while maintaining optimal protein-to-energy ratios to promote lean mass growth (Embleton 2007; Agostoni 2010; Johnston 2012; Moya 2012; Tudehope 2013). Multi-nutrient fortification may be especially important for infants who receive donated (donor) expressed breast milk, which contains lower levels of protein, energy and minerals than their own mother's expressed breast milk (Arslanoglu 2013). Commercially available fortifiers are expensive, and their use is less feasible in resource-poor settings in low- or middle-income countries (Chawla 2008; Kler 2015). An alternative strategy, more commonly employed in resource-limited settings, is to enrich breast milk by adding cow's milk formula powder to achieve the required level of nutrient enrichment (Gross 1993).

Targeted and adjustable fortification

Nutrient (especially energy and protein) content of expressed breast milk varies between mothers and between different batches of a woman's expressed breast milk (de Halleux 2013). If the nutrient levels in expressed breast milk are measured, the amount of fortifier added can be *targeted* (also referred to as *individualised*) to achieve a desired overall content (Rochow 2013; Rochow 2015). The level of fortification may be *adjusted* in response to the metabolic demands and responses of individual infants, for example, by titration to the infant's serum urea level (Arslanoglu 2010).

How the intervention might work

Feeding preterm infants with human milk fortified with energy and protein (as well as minerals and other nutrients) may be expected to promote nutrient accretion and growth (increase in weight, length and head circumference). Higher levels of nutrient intake during this critical period may be especially important for infants who are not able to consume larger quantities of milk, who have slow growth or who have ongoing additional nutritional and metabolic requirements (Agostoni 2010).

A potential disadvantage of multi-nutrient fortification is that increasing nutrient density and osmolarity of breast milk might interfere with gastric emptying and intestinal peristalsis, resulting in feed intolerance or increasing the risk of necrotising enterocolitis (Ewer 1996; McClure 1996; Gathwala 2008; Yigit 2008; Morgan 2011). Several cases of subacute bowel obstruction due to impaction with "milk curd" have been reported in very preterm infants fed with multi-nutrient fortified expressed breast milk, putatively due to the high calcium content causing fat malabsorption (Flikweert 2003; Wagener 2009; Stanger 2014). Investigators have been concerned that rapid growth with accelerated weight gain during this critical early phase might be associated with altered fat distribution and related 'programmed' metabolic consequences that may increase long-term risks of insulin resistance and hypertension (Euser 2005; Singhal 2007; Euser 2008).

Why it is important to do this review

Given the potential for multi-nutrient fortification of breast milk to affect important outcomes for preterm infants, this review aims to detect, appraise and synthesise available evidence from randomised controlled trials to inform practice and research.

OBJECTIVES

To determine whether multi-nutrient fortified human breast milk improves important outcomes (including growth and development) over unfortified breast milk for preterm infants without increasing the risk of adverse effects (such as feed intolerance and necrotising enterocolitis).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials, including cluster-randomised controlled trials. We did not include cross-over trials.

Types of participants

Preterm (< 37 weeks' gestational age) and low birth weight (< 2500 g) infants receiving enteral breast milk.

Types of interventions

Fortification of human breast milk (expressed maternal or donor or both) with both energy (carbohydrate or fat) *and* protein. Multi-nutrient fortifiers additionally could contain minerals, iron, vitamins or other nutrients. Multi-nutrient fortifiers could be cow (or another animal) milk-based or human milk-based. The control group should not have received energy *or* protein fortification but could have received milk supplemented with minerals, iron, vitamins or other nutrients.

Eligible trials should have planned to allocate the trial intervention for a sufficient period (at least two weeks) to allow measurable effects on growth. Infants in comparison groups within each trial should have received similar care other than the level of fortification of breast milk. No between-group differences in target levels of volume of milk intake should have occurred.

We did not include trials of:

- targeted fortification (vs standard fortification);
- adjustable fortification (vs standard fortification);
- early versus later introduction of multi-nutrient fortifier; or
- human milk-based versus cow milk-based fortifier.

Separate Cochrane reviews will consider these comparisons.

Types of outcome measures

Primary outcomes

- Growth: weight, length, head growth, skinfold thickness, body mass index and measures of body composition (lean/fat mass) and growth restriction (proportion of infants who remain < 10th percentile for the index population distribution of weight, length or head circumference).
- Neurodevelopmental outcomes assessed after 12 months post term: neurological evaluations, developmental scores and classifications of disability, including auditory and visual disability. We defined neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy, developmental quotient more than two standard deviations below the population mean and blindness (visual acuity < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification).

Secondary outcomes

- Duration of hospital admission (weeks).
- Feed intolerance that results in cessation or reduction in enteral feeding.
- Necrotising enterocolitis (modified Bell stage 2/3; Walsh 1986).
- Measures of bone mineralisation such as serum alkaline phosphatase level, or bone mineral content assessed by dual energy x-ray absorptiometry (DEXA) and clinical or radiological evidence of rickets on long-term follow-up (restricted to trials without mineral supplementation of the control group).
- Measures of long-term metabolic or cardiovascular health, including insulin resistance, obesity, diabetes and hypertension.

Search methods for identification of studies

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

Electronic searches

We searched MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Maternity and Infant Care (see Appendix 1).

We searched ClinicalTrials.gov and Current Controlled Trials for completed or ongoing trials.

Searching other resources

We examined the references in studies identified as potentially relevant. We also searched abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2015), the European Society for Paediatric Research (1995 to 2015), the UK Royal College of Paediatrics and Child Health (2000 to 2016) and the Perinatal Society of Australia and New Zealand (2000 to 2015). We considered trials reported only as abstracts to be eligible if sufficient information was available from the report, or from contact with study authors, to fulfil the inclusion criteria.

Data collection and analysis

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

Selection of studies

One review author (JB) screened titles and abstracts of all records identified by the search and coded records as "order" or "exclude". A second review author (WM) assessed all records coded as "order" and made the final decision about which records were ordered as full-text articles. JB read the full texts and used a checklist to assess each article's eligibility for inclusion on the basis of pre-specified inclusion and exclusion criteria. MM checked these decisions.

Data extraction and management

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

Assessment of risk of bias in included studies

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

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

- Random sequence generation: We categorised the method used to generate the allocation sequence as:
  - low risk - any truly random process (e.g. random number table, computer random number generator);
  - high risk - any non-random process (e.g. odd or even date of birth, hospital or clinic record number); or
  - unclear risk - no or unclear information provided.

- Allocation concealment: We categorised the method used to conceal the allocation sequence as:
  - low risk (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
  - high risk - open random allocation (e.g. unsealed or non-opaque envelopes, alternation, date of birth); or
  - unclear risk - no or unclear information provided.

- Blinding: We assessed blinding of participants, clinicians, caregivers and outcome assessors separately for different outcomes and categorised the methods as:
  - low risk;
  - high risk; or
  - unclear risk.

- Incomplete outcome data: We described the completeness of data from the analysis including attrition and exclusions for each outcome and reasons for attrition or exclusion, when reported. We assessed whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by the trial authors, we planned to reinstate missing data in the analyses. We categorised completeness as:
  - low risk: $\leq$ 10% missing data;
  - high risk: > 10% missing data; or
  - unclear risk: no or unclear information provided.

Measures of treatment effect

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

Unit of analysis issues

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

Dealing with missing data

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

Assessment of heterogeneity

We examined treatment effects in individual trials and heterogeneity between trial results by inspecting the forest plots if more than one trial was included in a meta-analysis. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. If we detected substantial ($I^2 > 50\%$) heterogeneity, we explored possible causes (e.g. differences in study design, participants, interventions or completeness of outcome assessments) in sensitivity analyses.

Assessment of reporting biases

We inspected funnel plots for asymmetry if more than five trials were included in a meta-analysis.

Data synthesis

We used a fixed-effect model for meta-analyses.

Quality of evidence

We assessed the quality of evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). This considers evidence from randomised controlled trials as high quality that may be downgraded on the basis of consideration of any of five areas.

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

The GRADE approach results in assessment of the quality of a body of evidence according to four grades (Schünemann 2013).

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

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

In cases for which we considered risk of bias arising from inadequate concealment of allocation, randomised assignment, complete follow-up or blinded outcome assessment to reduce our confidence in the effect estimates, we downgraded the quality of evidence accordingly (Guyatt 2011b). We evaluated consistency on the basis of similarity of point estimates, extent of overlap of confidence intervals and statistical criteria, including measurement of heterogeneity (I^2). We downgraded the quality of evidence when inconsistency across study results was large and unexplained (i.e. some studies suggested important benefit, and others no effect or harm with no explanation) (Guyatt 2011c). We assessed precision accordingly with the 95% confidence interval (CI) around the pooled estimation (Guyatt 2011d). When trials were conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness (Guyatt 2011e).

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

Subgroup analysis and investigation of heterogeneity

We planned to undertake these subgroup analyses, when possible.

- Very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants (vs infants 32 to 36 weeks' gestation or birth weight 1500 to 2499 g).
- Fortifcation of donor breast milk (vs maternal expressed breast milk).
- Trials using fortifier extracted from human milk (vs cow milk-based fortifier).
- Trials supplementing breast milk with infant formula (vs cow milk-based fortifier).
- Trials conducted in low- and middle-income countries versus high-income countries (see http://data.worldbank.org/about/country-classifications).

RESULTS

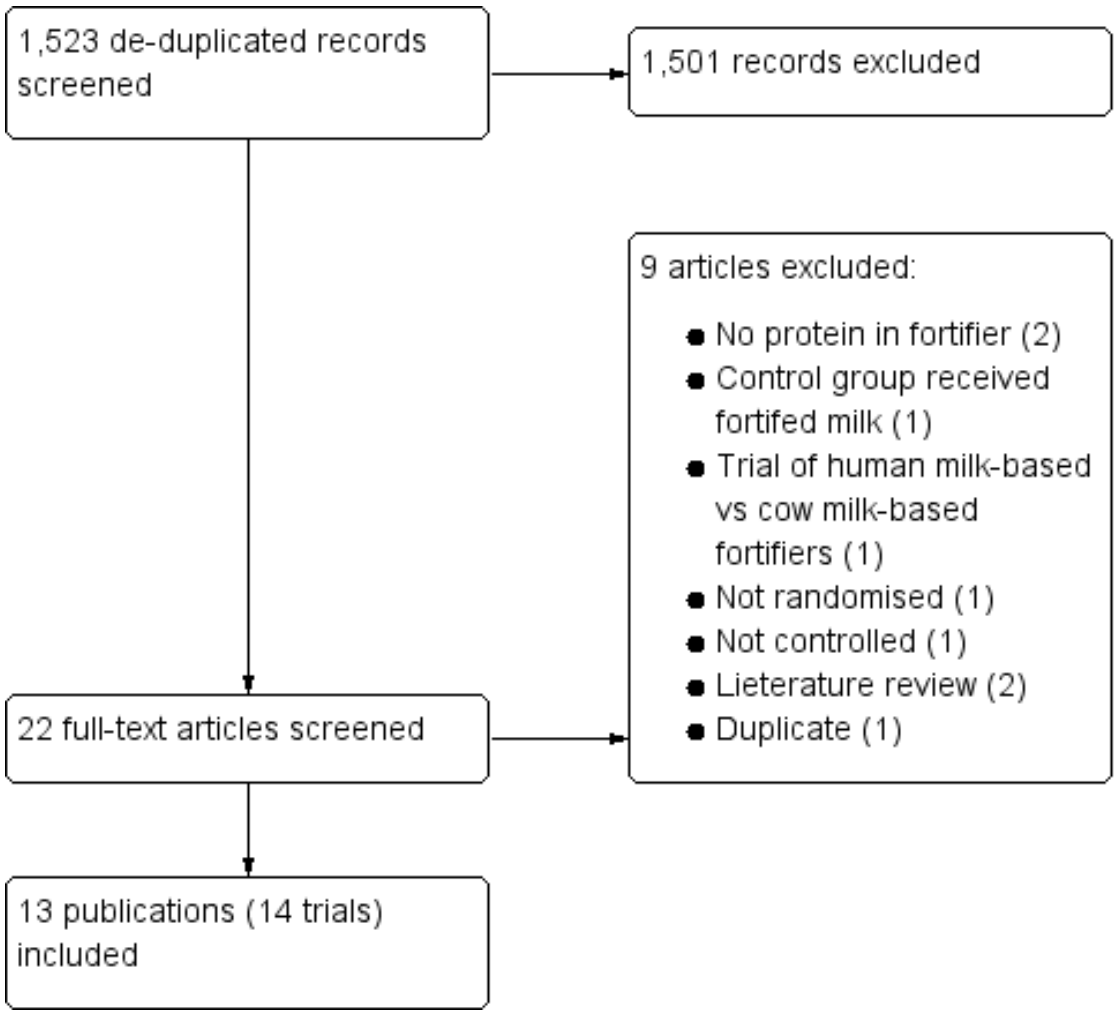
Description of studies

See also Characteristics of included studies and Characteristics of excluded studies.

Results of the search

See Figure 1 for an illustration of the study selection process.

Figure 1. Flow diagram.



Included studies

We included in this review 14 trials (13 primary publications) in which 1071 infants participated that met our inclusion criteria (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Polberger 1989; Porcelli 1992; Zuckerman 1994; Lucas 1996; Wauben 1998; Nicholl 1999; Faerk 2000; Bhat 2003; Mukhopadhyay 2007; Gathwala 2012). Sample sizes ranged between 14 and 275 participants.

All trials were set in specialist paediatric hospital settings, mainly neonatal intensive care units. Ten trials were single-centre trials (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Porcelli 1992; Zuckerman 1994; Nicholl 1999; Bhat 2003; Mukhopadhyay 2007; Gathwala 2012), and each of the remaining four was conducted at two centres (Polberger 1989; Lucas 1996; Wauben 1998; Faerk 2000).

We noted that five trials were conducted in Europe (Polberger 1989; Porcelli 1992; Lucas 1996; Nicholl 1999; Faerk 2000), four in North America (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Wauben 1998), three in Asia (Bhat 2003; Mukhopadhyay 2007; Gathwala 2012) and two in Africa (Pettifor 1989; Zuckerman 1994). Publication dates span four decades, ranging from 1986 to 2012.

Participants

All trials included preterm or low birth weight infants and excluded those with major congenital abnormalities. Eight trials restricted participation to very preterm or VLBW infants (Modanlou 1986; Pettifor 1989; Polberger 1989; Zuckerman 1994; Nicholl 1999; Faerk 2000; Bhat 2003; Mukhopadhyay 2007). The other trials specified the following as an upper birth weight eligibility criterion:

- 1600 g (Gross 1987 (1); Gross 1987 (2)).
- 1800 g (Gathwala 2012; Wauben 1998).
- 1850 g (Lucas 1996).
- 2000 g (Porcelli 1992).

Average gestational age of included infants across all trials was 30 weeks. The nature of the intervention required that babies in all trials must tolerate enteral feeds and mothers needed to supply expressed breast milk.

Interventions

For all infants, trials relied largely on provision of the mother's own expressed breast milk. Three trials used only the mother's own milk (Pettifor 1989; Zuckerman 1994; Wauben 1998). It was not always reported how feeds were made up if the mother could not provide sufficient milk, but in some studies, infants were excluded on this basis. Seven trials supplemented mother's own milk with donor (or "bank") milk (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Porcelli 1992; Nicholl 1999; Faerk 2000; Mukhopadhyay 2007). Investigators in the remaining four trials used formula to top feeds up to the required volume (Modanlou 1986; Lucas 1996; Bhat 2003; Gathwala 2012).

Types of multi-nutrient fortification added to milk for infants in the intervention groups varied. Most trials used a commercially available, cow's milk-based, powdered preparation containing varying amounts of protein, fat, carbohydrate, minerals, electrolytes and trace minerals.

- Similac Human Milk Fortifier (HMF; Ross Laboratories): Gross 1987 (1); Gross 1987 (2) [Gross 1987 (1) included a third group of infants receiving human milk fortified with formula (see below).
- FM85 (Nestlè): Porcelli 1992.
- Enfamil HMF (Mead Johnson): Lucas 1996.
- Nutriprem (Cow & Gate Nutricia): Nicholl 1999.
- Eoprotin (Milupa): Faerk 2000.
- Lactodex HMF (Raptakos Brett): Mukhopadhyay 2007; Gathwala 2012.
- Trial-specific multi-nutrient fortifier (Wyeth-Ayerst): Wauben 1998.

Two trials mixed equal volumes of human milk and preterm formula.

- Similac Special Care, Ross Laboratories: Gross 1987 (1).
- Alprem (Nestlè): Zuckerman 1994.

Three trials did not specify the name or manufacturer of the multi-nutrient fortifier used: Modanlou 1986; Polberger 1989; Bhat 2003.

All trials used a fixed, pre-specified amount of fortifier for all infants in the intervention group. Some trials titrated the amount of fortifier per feed to try to prevent feed intolerance.

Comparators

Most trials added vitamins, minerals or other nutrients to control infants' feeds as part of standard hospital practice. Four trials provided all infants with additional vitamin D (Pettifor 1989; Porcelli 1992; Zuckerman 1994; Faerk 2000). Five trials provided all infants with several vitamins and minerals (added to feeds for infants in the control group, and included in the fortifier or added separately for infants in the intervention group) (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Lucas 1996; Wauben 1998). Researchers in five trials gave no supplements at all to control group infants (Modanlou 1986; Nicholl 1999; Bhat 2003; Mukhopadhyay 2007; Gathwala 2012).

Outcomes

Investigators in all included trials assessed at least one of our prespecified outcomes of interest. Ten trials contributed growth rate data (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Polberger 1989; Porcelli 1992; Lucas 1996; Wauben 1998; Nicholl 1999; Mukhopadhyay 2007). Only Lucas 1996 reported size and neurodevelopmental data at follow-up beyond hospital discharge.

Excluded studies

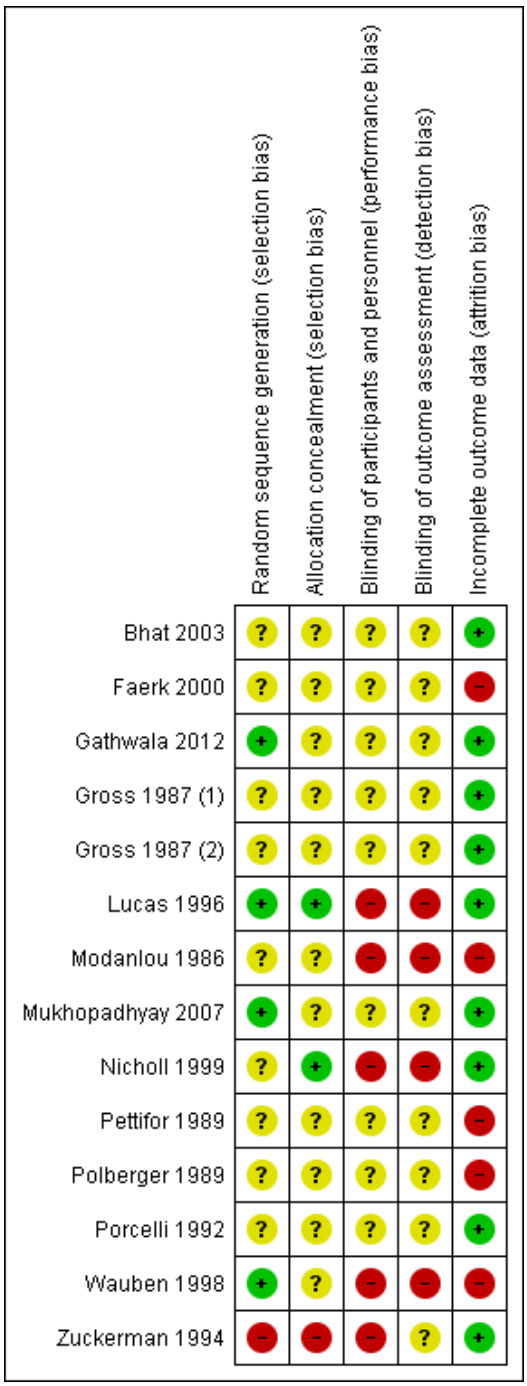
See Characteristics of excluded studies for details. We excluded:

- Carey 1987 and Greer 1988 because they used fortification with protein only (no fortification with fat or carbohydrate);
- Tarcan 2004; Arslanoglu 2009; Reali 2010; and Hair 2014 because they were not randomised controlled trials; and
- Abrams 2014 because it compared human versus cow's milk-based protein fortification rather than fortification versus no fortification.

Risk of bias in included studies

Overall, we found risk of bias difficult to assess as the result of limited reporting. Consequently, we scored most items as "unclear" (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Risk of selection bias was largely unclear. Only four trials described adequate methods of random sequence generation (Lucas 1996; Wauben 1998; Mukhopadhyay 2007; Gathwala 2012). Only two explicitly described adequate allocation concealment methods (Lucas 1996; Nicholl 1999). Zuckerman 1994 was at high risk of selection bias, as investigators performed group allocation in a quasi-randomised fashion (odd and even hospital numbers).

Blinding

Risk of performance and selection bias was also unclear in most trials. Several trials were known to be at high risk as reports stated that personnel and outcome assessors were not blinded (Modanlou 1986; Zuckerman 1994; Lucas 1996; Wauben 1998; Nicholl 1999).

Incomplete outcome data

We judged five trials to be at high risk of attrition bias (Modanlou 1986; Pettifor 1989; Polberger 1989; Wauben 1998; Faerk 2000) and all other trials to be at low risk.

Other potential sources of bias

Authors of three trials were employees of the manufacturer of the fortifier used (Modanlou 1986; Lucas 1996; Wauben 1998). The manufacturer of the fortifier used funded two trials (Pettifor 1989; Lucas 1996).

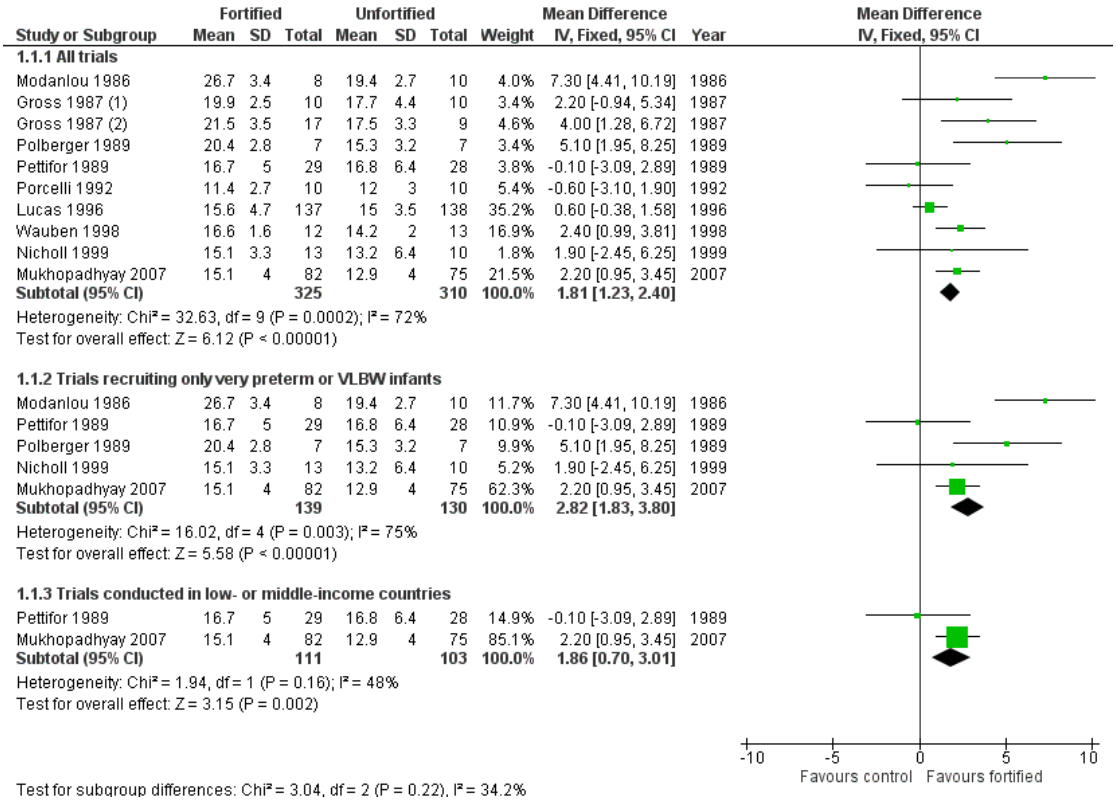
Effects of interventions

See: **Summary of findings for the main comparison** Multi-nutrient fortification of human milk for preterm infants

Growth rates (Outcomes 1.1 to 1.6)

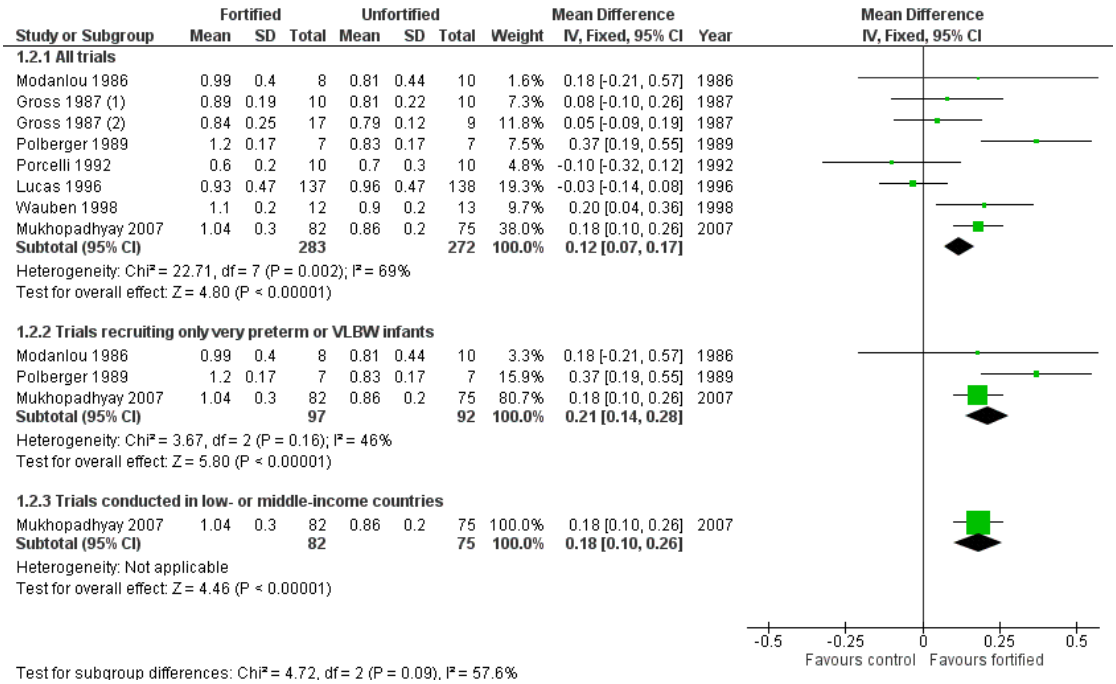
Weight gain (Analysis 1.1): We obtained data from 10 trials including 635 infants (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Polberger 1989; Porcelli 1992; Lucas 1996; Wauben 1998; Nicholl 1999; Mukhopadhyay 2007). Several trials as well as a meta-analysis of the data from all trials showed a statistically significantly higher rate of weight gain in the intervention (fortifier) group (MD 1.81, 95% CI 1.23 to 2.40 g/kg/d). Substantial heterogeneity was present in this analysis (I^2 = 72%) (Figure 3).

Figure 3. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.1 Weight gain (g/kg/d).



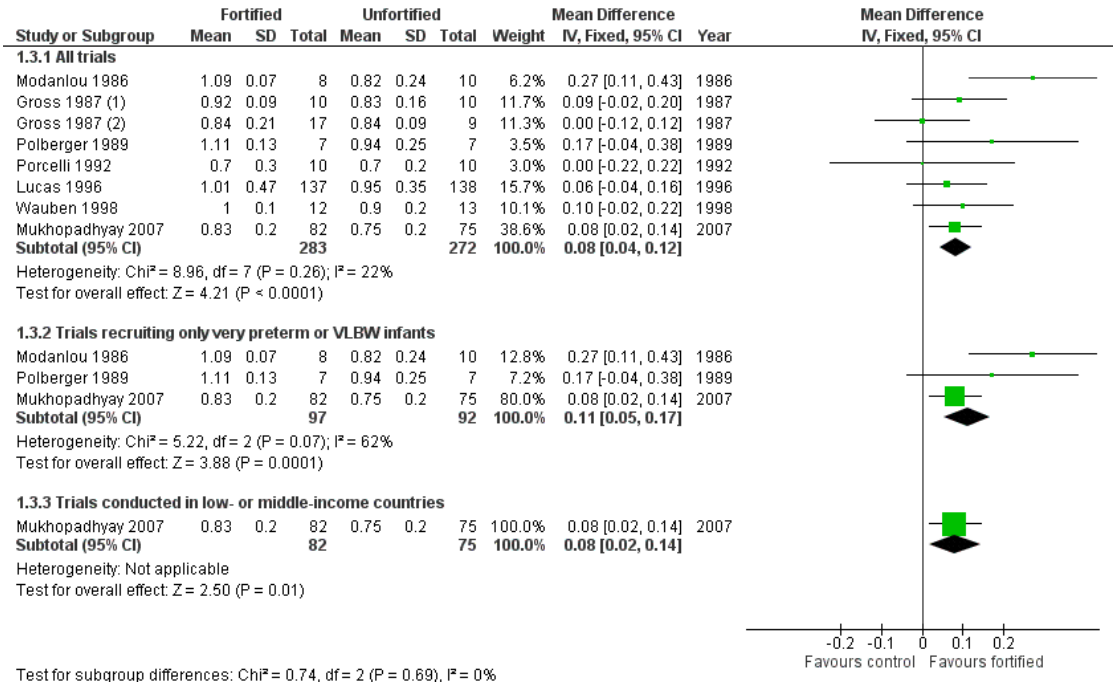
Length gain (Analysis 1.2): We obtained data from eight trials including 555 infants (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Polberger 1989; Porcelli 1992; Lucas 1996; Wauben 1998; Mukhopadhyay 2007). Results across individual trials varied, but a meta-analysis of the data from all trials showed a statistically significantly higher rate of length gain in the fortified group (MD 0.18, 95% CI 0.10 to 0.26 cm/wk). We detected substantial heterogeneity in this analysis (I^2 = 69%) (Figure 4).

Figure 4. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.2 Length gain (cm/wk).



Head growth (Analysis 1.3): We obtained data from eight trials including 555 infants (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Polberger 1989; Porcelli 1992; Lucas 1996; Wauben 1998; Mukhopadhyay 2007). Results across individual trials varied, but a meta-analysis of the data from all trials showed a statistically significantly higher rate of head growth in the intervention group (MD 0.08, 95% CI 0.04 to 0.12 cm/wk). We detected low heterogeneity in this analysis (I^2 = 22%) (Figure 5).

Figure 5. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.3 Head growth (cm/wk).



Weight at 12 to 18 months (Analysis 1.4): We obtained data from Lucas 1996 and Wauben 1998 (270 infants). Neither trial nor a meta-analysis of the data from both trials showed a statistically significant difference (MD -0.03, 95% CI -0.31 to 0.25 kg).

Length at 12 to 18 months (Analysis 1.5): We obtained data from Lucas 1996 and Wauben 1998 (270 infants). Neither trial nor a meta-analysis of the data from both trials showed a statistically significant difference (MD -0.19, 95% CI -0.98 to 0.60 cm).

Head circumference at 12 to 18 months (Analysis 1.6): We obtained data from Lucas 1996 and Wauben 1998 (270 infants). Neither trial nor a meta-analysis of the data from both trials showed a statistically significant difference (MD 0.10, 95% CI -0.37 to 0.18 cm).

Neurodevelopmental outcomes after 12 months of age (Outcomes 1.7 and 1.8)

Only one trial (245 infants) reported data on this outcome (Lucas 1996). This trial reported no statistically significant differences in:

- mental development index at 18 months (Analysis 1.7): MD 2.20 (95% CI -3.35 to 7.75); nor
- psychomotor development index at 18 months (Analysis 1.8): MD 2.40 (95% CI -1.90 to 6.70).

Length of hospital stay in weeks (Outcome 1.9)

We obtained data from Zuckerman 1994 and Mukhopadhyay 2007 (210 infants) (Analysis 1.9). Neither trial nor a meta-analysis of their data showed a statistically significant difference (MD 0.38, 95% CI -0.16 to 0.93 weeks).

Feed intolerance (Outcome 1.10)

We obtained data from five trials (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Wauben 1998; Mukhopadhyay 2007) including 255 infants (Analysis 1.10). Results across individual trials varied, and a meta-analysis of data showed no statistically significant differences (typical RR 0.90, 95% CI 0.54 to 1.49).

Necrotising enterocolitis (Outcome 1.11)

We obtained data from 11 trials (Modanlou 1986; Pettifor 1989; Polberger 1989; Porcelli 1992; Zuckerman 1994; Lucas 1996; Wauben 1998; Nicholl 1999; Faerk 2000; Bhat 2003; Mukhopadhyay 2007) including 882 infants (Analysis 1.11). Results across individual trials varied, and a meta-analysis of the data from all trials showed no statistically significant differences (typical RR 1.57, 95% CI 0.76 to 3.23).

Measures of bone mineralisation (Outcomes 1.12 and 1.13)

Serum alkaline phosphatase (Analysis 1.12): Meta-analysis of data obtained from five trials (restricted to trials without mineral supplementation of the control group) showed that the intervention group had statistically significantly lower serum alkaline phosphatase (ALP) levels (Modanlou 1986; Pettifor 1989; Zuckerman 1994; Mukhopadhyay 2007; Gathwala 2012): weighted mean difference (WMD) -126 (95% CI -191 to -62) IU/L. Substantial heterogeneity was present in this analysis (I^2 = 58%). Bhat 2003 did not report peak ALP levels but did state that the intervention group included fewer infants who developed high ALP levels (> 450 IU/L) than were included in the control group (without mineral supplementation).

Bone mineral content (Analysis 1.13): Only Pettifor 1989 provided numerical data and reported a statistically significantly higher level of bone mineral content in the intervention group: WMD 12.0 (95% CI 6.3 to 17.7) mg/cm. Modanlou 1986, Gross 1987 (1) and Gross 1987 (2) detected no statistically significant differences between control and treatment groups but did not report numerical data for inclusion in meta-analyses.

Measures of metabolic health on long-term follow-up

No included trials reported these measures.

Subgroup analyses

Very preterm or VLBW infants

Meta-analyses of data from trials that restricted participation to very preterm or VLBW infants showed no substantial differences in meta-analyses of all trial data (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13).

Fortifcation of donor breast milk

Seven trials supplemented mother's own milk with donor (or "bank") milk (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Porcelli 1992; Nicholl 1999; Faerk 2000; Mukhopadhyay 2007). None of these investigators used donor milk exclusively (or predominantly), and none reported subgroup data for infants fed with donor breast milk exclusively.

Trials using fortifier extracted from human milk (rather than cow's milk-based fortifiers)

All trials included in this review used cow's milk-based fortifiers.

Trials supplementing breast milk with infant formula (rather than breast milk fortifier)

Gross 1987 (2) (for a subset of the intervention group, N = 19) and Zuckerman 1994 (N = 56) used preterm infant formula to fortify breast milk in their trials. Gross 1987 (2) reported in-hospital growth parameters and found effects consistent with the meta-analyses. Zuckerman 1994 reported data on length of hospital stay, incidence of necrotising enterocolitis and levels of serum ALP consistent with the meta-analyses (Analysis 1.9; Analysis 1.11; Analysis 1.12).

Trials conducted in low- and middle-income countries

Researchers conducted four trials in middle-income countries: Pettifor 1989 and Zuckerman 1994 in South Africa (upper middle-income country) and Mukhopadhyay 2007 and Gathwala 2012 in India (lower middle-income country). Meta-analyses were limited and showed no substantial differences from the meta-analyses of all trials together (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13).

DISCUSSION

Summary of main results

Available evidence from 14 randomised controlled trials suggests that multi-nutrient fortification (both energy and protein, as well as minerals and vitamins) results in small but statistically significant increases in rates of weight gain, length gain and head growth for preterm infants. However, most trials reported growth parameters only over short-term study periods during the initial neonatal unit admission. Very few data are available for growth and developmental outcomes assessed beyond infancy, and these show no statistically significant effects of fortification. None of these trials have reported data related to possible longer-term "programmed" metabolic or physiological consequences of multi-nutrient supplementation in early infancy.

Meta-analysis of data from trials that included a control group without bone mineral supplementation showed that multi-nutrient fortification reduces serum alkaline phosphatase (ALP) levels but provided limited evidence of effects on other measures of bone mineralisation or health. This review found no consistent evidence of other potential benefits or harms of fortification, including no data to suggest that fortification increases the risk of feed intolerance or necrotising enterocolitis in preterm infants.

Overall completeness and applicability of evidence

We recommend cautious interpretation and application of these findings. Although meta-analyses indicate that multi-nutrient fortification increases rates of growth, typical effect sizes are very modest. Over the course of four weeks, multi-nutrient fortification for a very preterm infant weighing 1 kg at birth would result in an extra 50 g of weight gain, 7 mm of length gain and 3 mm of head circumference gain. As well as uncertainty about the clinical importance of these small effects on hospital growth rates, considerable uncertainty remains about longer-term impact on growth or development. Similarly, although multi-nutrient fortification that includes minerals (vs breast milk without added minerals) reduces the serum ALP level, this in itself is an insensitive measure of bone mineralisation or health (Tinnion 2012). Furthermore, in current clinical practice, mineral supplements (mainly phosphate) are available for infants at high risk of, or with biochemical or other features of, metabolic bone disease.

Meta-analyses of growth outcomes showed substantial statistical heterogeneity that was not explained by major differences in trial design or conduct. Participants in these trials were similar (mostly stable VLBW infants). Although we noted some variation in types of fortifier used, the overall target level of multi-nutrient fortification was similar. Most trials aimed to provide extra energy, protein and minerals by adding a powdered, commercially available multi-nutrient fortifier to breast milk to attain 75 to 80 kcal/100 mL and about 2.0 to 2.6 g of protein/100 mL (plus proportionate supplements of minerals, vitamins and trace elements). This approach maintained optimal protein-to-energy ratios to ensure that the protein contributed to growth and was not catabolised as a fuel source (Kashyap 1994). However, these total levels of protein and energy fortification are at the lower bounds of current recommended intakes needed to match intrauterine accretion (based on receiving about 150 mL/kg/d of milk), and this is a likely explanation for the limited impact of the intervention on growth parameters. These findings are broadly consistent with those of another Cochrane review which found that formula-fed preterm infants who received higher levels of protein (> 3 g/kg/d) gained weight about 2.4 g/kg/d faster than infants who received standard levels of protein (Fenton 2014).

A final major limitation of this review is that most included trials were undertaken at healthcare facilities in high-income countries, and none in community settings or low-income countries. Reported evidence therefore may be of limited use to inform care practice in the resource-limited settings where most preterm and low birth weight infants are cared for globally (Imdad 2013).

Quality of the evidence

We assessed the quality of the evidence as low or moderate for most outcomes (Summary of findings for the main comparison). Included trials were small and were generally of low methodological quality, yielding no evidence of use of adequate measures to conceal random allocation and incomplete follow-up assessment during the intervention period. Blinding of participants and caregivers was not possible given the nature of the intervention, but this is not likely to be a major source of bias in growth assessments. Knowledge of the intervention group may have affected caregivers' or mothers' perceptions and views of feeding, and may have influenced decisions on whether any formula should be given as a supplement to (or instead of) breast milk. These trials did not examine whether multi-nutrient fortification affected the mother's commitment to establish breast feeding, or whether differences were noted in the proportion of infants receiving any breast milk at the end of the intervention period.

Potential biases in the review process

Our main concern with the review process is the possibility that findings are subject to publication and other reporting biases. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and searching the proceedings of major international perinatal conferences to identify trial reports that are not (or are not yet) published in full form in academic journals. The meta-analyses that we performed did not contain sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

Multi-nutrient fortification of human milk is associated with small, short-term increases in weight gain and in linear and head growth. No evidence suggests that these short-term gains in growth lead to any long-term effects on growth or development. Investigators reported no increase in adverse effects among infants who received multi-nutrient fortifiers, although the total number of infants studied was small and the data that could be abstracted from published studies were limited.

Implications for research

Given the potential for multi-nutrient fortification of breast milk to affect important outcomes in preterm infants, this intervention merits further assessment. As this practice is already widely established and accepted as a standard of care in many neonatal units, it is important for researchers to determine whether mothers and clinicians would support a trial of this intervention. All trials should be powered to detect potentially important effects on growth rates, as well as potential adverse consequences, during infancy and beyond. Trials should attempt to ensure that caregivers and assessors are blind to the intervention. Although this goal is more easily achievable for longer-term assessments, it is

also important for ascertainment of adverse events, such as feeding intolerance and necrotising enterocolitis, when the threshold for investigation or diagnosis may be affected by knowledge of the intervention. We have identified one such planned trial (Mills 2015).

New research areas

Most commercially available fortifiers contain varying amounts of protein, carbohydrate, calcium, phosphate, other minerals (zinc, manganese, magnesium and copper), vitamins and electrolytes. Investigators have not evaluated the benefits of many of these individual components in a controlled manner. In the future, researchers could compare different proprietary preparations to evaluate both short-term and long-term outcomes and adverse effects, while searching for the "optimal" composition of fortifiers. Investigators could also examine the effects of targeted or adjustable fortification to determine whether human milk-based fortifier provides any (cost-effective) advantages over cow's milk-based fortifier.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bhat 2003

Methods	Randomised controlled trial
Participants	100 VLBW infants Excusion criterion: need for prolonged mechanical ventilation Setting: Special Care Baby Unit, Khoula Hospital, Muscat, Oman
Interventions	Intervention (N = 50): fortified human milk (4 g of powdered fortifier to achieve 81 kcal, 2.4 g protein, 9.0 g carbohydrates per 100 mL of milk) Control (N = 50): human milk only If amounts were insufficient, human milk was supplemented with formula up to a maximum of 15% of energy for 2 days. Babies who required supplementation beyond this were excluded from the study
Outcomes	• Weight gain • Markers of nutritional and bone mineral status • Adverse events including necrotising enterocolitis
Notes	Human milk was enriched with a fortifier after babies reached a volume of 140 mL/kg/d by the enteral route

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as "double-blind", but it was not specified who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was described as "double-blind", but it was not specified who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Faerk 2000

Methods	Randomised controlled trial
Participants	103 very preterm infants Excusion criterion: major congenital anomaly Setting: NICUs, Rigshospitalet and Hvidovre Hospital, Copenhagen, Denmark
Interventions	Intervention (N = 51): human milk (maternal or donor) supplemented with 0.4 g protein, 1.4 g carbohydrate, 35 mg calcium and 17 mg phosphorus per 100 mL (Milupa Eoprotin) Control (N = 52): maternal or donor milk supplemented with 10 mg phosphate per 100 mL
Outcomes	• Weight, length and head circumference at term • Measures of bone mineralisation (DEXA scan) • Necrotising enterocolitis
Notes	Target intake of 200 mL/kg/d All infants received vitamin D 800 IU per day Intervention ceased when breast-fed or at 36 weeks' postmenstrual age

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is described as "double-blind", but it was not specified who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is described as "double-blind", but it was not specified who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	103 infants were randomised, but outcome data were reported for only 76 (74%) because of loss to follow-up or technical problems with DEXA scans. Further information about outcomes was not available from investigators

Gathwala 2012

Methods	Randomised controlled trial
Participants	67 consecutive preterm infants of birth weight < 1800 g Eligibility criteria: healthy preterm infants, appropriate for gestational age, no birth asphyxia, enterally fed with breast milk by 14 days of life, no congenital malformations, no ventilatory support previous 7 days, no diuretic or steroid therapy Setting: Neonatology Unit, Department of Paediatrics, Pt. B.D. Sharma PGIMS, Rohtak, India
Interventions	Intervention (N = 34): breast milk fortified with Lactodex Human Milk Fortifier (to achieve 80 kcal, 9.4 g carbohydrate, 2.2 g protein per 100 mL, plus minerals and electrolytes) Control (N = 33): unfortified breast milk Infants were excluded from the study if they needed more than 25% of their daily requirements to be provided by formula or other milk
Outcomes	• Time to regain birth weight • Time to reach 2200 g • Duration of hospital stay • Biochemical markers of nutritional status (including serum ALP)
Notes	Incidence of feed intolerance or necrotising enterocolitis not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a random numbers table
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four babies in the intervention group and 3 in the control group were excluded post randomisation, as their need for additional milk exceeded 25%. These infants were not included in intention-to-treat analyses

Gross 1987 (1)

Methods	Randomised controlled trial (2-phase trial, referred to as Gross 1987 (1) and Gross 1987 (2))
Participants	20 infants with birth weight < 1600 g Eligibility criteria: birth weight appropriate for gestational age, free from congenital anomaly or major disease, breathing room air, ability to begin enteral feeding within first week after birth Setting: Duke University Medical Center, Durham, North Carolina, USA
Interventions	Intervention (N = 10): human milk mixed with premature infant formula Similac Special Care (Ross Laboratories) containing 1.8 g protein per 100 mL, as well as carbohydrate Control (N = 10): human milk with no supplementation Feeding of human milk supplemented with formula commenced after 1 week of enteral feeds of unfortified human milk. All infants received intravenous dextrose and electrolytes until day 5 of feeding. All infants received supplemental vitamins with their milk from day 8 of feeding
Outcomes	• In-hospital growth parameters • Growth at 44 weeks' postmenstrual age • Bone mineral content and biochemical indices of bone metabolism
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not reported. Report states that infants were "assigned randomly" to receive fortified or unfortified breast milk
Allocation concealment (selection bias)	Unclear risk	Report states that "sealed envelopes" were used, but it is unclear whether these were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Gross 1987 (2)

Methods	Randomised controlled trial (2-phase trial, referred to as Gross 1987 (1) and Gross 1987 (2))
Participants	30 infants with birth weight < 1600 g Eligibility criteria: birth weight appropriate for gestational age, free from congenital anomaly or major disease, breathing room air, ability to begin enteral feeding within first week after birth Setting: Boston Perinatal Center, Boston, Massachusetts, USA
Interventions	Intervention 1 (N = 11): human milk mixed with premature infant formula Similac Special Care (Ross Laboratories) containing 1.8 g protein per 100 mL, as well as carbohydrate (as above for Gross 1987 (1)) Intervention 2 (N = 10): human milk mixed with powdered breast milk fortifier Control (N = 9): human milk with no supplementation Fortification with the powdered fortifier was introduced after 2 weeks of enteral feeds of unfortified human milk. All infants received intravenous dextrose and electrolytes until day 5 of feeding. All infants received supplemental vitamins with their milk from day 8 of feeding. For this review, participants from the 2 intervention groups were taken together as infants receiving fortification
Outcomes	• In-hospital growth parameters • Growth at 44 weeks' postmenstrual age • Bone mineral content and biochemical indices of bone metabolism
Notes	The full composition of powdered fortifier was not reported in the paper. Following our own Internet research, we deemed it appropriate for inclusion, as powdered fortifier appeared to include protein and energy, as required by our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation not reported. Report states that infants were "assigned randomly" to receive fortified or unfortified breast milk
Allocation concealment (selection bias)	Unclear risk	Report states that "sealed envelopes" were used, but it is unclear whether these were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded

Gross 1987 (2) (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Four infants (2 in intervention group 1, and 2 in intervention group 2) did not complete the study because of feed intolerance. Results of growth outcomes for these infants were not presented

Lucas 1996

Methods	Randomised controlled trial
Participants	275 preterm infants with birth weight < 1850 g Eligibility criteria: no major congenital abnormalities, resident in UK, mother agreed to provide breast milk Setting: 2 centres in Cambridge and Norwich, UK
Interventions	Intervention (N = 137): maternal milk supplemented with (per 100 mL) 0.7 g protein (bovine), 2.73 g carbohydrate, 0.05 g fat, 90 mg calcium and 45 mg phosphate, as well as electrolytes (Enfamil, Mead Johnson) Control (N = 138): maternal milk supplemented with 15 mg/100 mL phosphate Enteral intake 180 mL/kg/d Intervention ceased at discharge, or when weight reached 2000 g All infants received vitamins (including vitamin D 260 IU/100 mL) Infants whose mothers could not provide sufficient milk were supplemented with a preterm formula and were not excluded from the analysis
Outcomes	• In-hospital growth rates • Growth to 9 and 18 months • Neurodevelopmental outcomes at 9 and 18 months • Serum indices of bone metabolism • Necrotising enterocolitis
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of permuted blocks of randomised length
Allocation concealment (selection bias)	Low risk	Use of sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded

Lucas 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded (except for assessment of neurodevelopmental outcomes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Modanlou 1986

Methods	Randomised controlled trial
Participants	39 infants of birth weight between 1000 and 1500 g Eligibility criteria: birth weight appropriate for gestational age, no ventilatory assistance after 7 days, no supplemental oxygen after 10 days, fewer than 3 days of diuretic therapy, enteral feeding by 14 days after birth Setting: Miller Children's Hospital of Long Beach, California, USA
Interventions	Intervention (N = 20): mother's own milk plus fortifier (to provide supplemental 0.7 g protein, 2.7 g carbohydrate, "trace" fat, 60 mg calcium and 33 mg phosphate per 100 mL of breast milk) Control (N = 19): mother's own milk Formula and human milk were diluted initially and the fortifier added gradually to milk for infants in the intervention group to reach target calorific density over 7 days (approximately) in all groups. Milk was generally provided by intermittent bolus gavage until nipple feedings were tolerated. Infants received standard infant formula if their mother's milk was unavailable for "an occasional feeding" (up to a maximum of 10% of feedings per week)
Outcomes	• Growth rates (weight, length, head circumference) • Feeding intolerance and necrotising enterocolitis • Biochemical status • Bone mineral content
Notes	Intervention ceased at discharge, or when weight reached 1800 g

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Report states that sealed envelopes were used. It is not reported whether these were sequentially numbered and opaque

Modanlou 1986 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	19 infants left the study after randomisation because of "insufficient maternal milk supply", and another 2 infants were withdrawn because of suspected NEC. Outcome data for inclusion in intention-to-treat analyses were not available for these infants

Mukhopadhyay 2007

Methods	Randomised controlled trial
Participants	166 VLBW infants (and gestational age < 35 weeks at birth) Eligibility criteria: feed volume of 150 mL/kg/d, feeds consisting of at least 80% breast milk, no congenital malformations nor gastrointestinal abnormalities Setting: PGIMER, Chandigarh, India
Interventions	Intervention (N = 85): breast milk fortified with Lactodex Human Milk Fortifier (2 g sachet per 50 mL of milk: 0.2 g protein, 1.2 g carbohydrate, 6.5 kcal energy) Control (N = 81): breast milk with added vitamins and minerals
Outcomes	• Growth rates (weight, length, head circumference) • Biochemical parameters • Length of hospital stay • Feeding intolerance and necrotising enterocolitis
Notes	Fortification was stopped once babies reached a weight of 2000 g or were fully breastfed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a random numbers table
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether personnel were blinded (participant blinding irrelevant in this context)

Mukhopadhyay 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Nicholl 1999

Methods	Randomised controlled trial
Participants	23 VLBW infants receiving enteral feeds of at least 150 mL/kg/d Eligibility criteria: no fluid restriction, no diuretics, no postnatal systemic steroid use, no significant congenital abnormality Setting: neonatal intensive care unit, Kings College Hospital, London, UK
Interventions	Intervention (N = 13): maternal (or pasteurised pooled donor milk) supplemented (per 100 mL) with 0.7 g protein, 2.0 g carbohydrate, 30 mg calcium, 40 mg phosphorus, trace minerals and vitamins Control (N = 10): unsupplemented maternal or donor milk Intervention ceased when infants no longer required nasogastric feeds
Outcomes	• In-hospital growth parameters • Indices of bone metabolism
Notes	Intervention ceased when infants no longer required nasogastric feeds One infant whose mother declined fortifier was included in results of non-fortified infants, and one baby whose mother preferred the addition of fortifier was included in results of the intervention group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomized", but method of sequence generation was not described
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded

Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Pettifor 1989

Methods	Randomised controlled trial
Participants	100 consecutive infants weighing between 1000 and 1500 g at birth Eligibility criteria: no major congenital abnormalities or metabolic disturbances, no requirement for ventilation at the point of entry into the study (day 4 after birth), free from serious infection, receiving at least 45 mL/kg/d of gavage feedings (expressed breast milk) at the beginning of the study Setting: Baragwanath Hospital, Bertsham, South Africa
Interventions	Intervention (N = 53): mother's own milk supplemented with (per 100 mL) 0.05 g protein, 1.1 g carbohydrate, 0.26 g fat, 72.3 mg calcium and 34 mg phosphate, along with electrolytes and vitamins (HMF, Ross Laboratories) Control (N = 47): mother's own milk Feeds were titrated as tolerated up to 200 mL/kg/d. Feeds were delivered by nasogastric tube until infants weighed 1600 g. At this point, bottle feeding was introduced gradually. Infants were removed from the study if their mother could not supply sufficient breast milk
Outcomes	• Weight gain • Serum calcium, phosphorus, alkaline phosphatase and albumin levels • Bone mineral homeostasis • Necrotising enterocolitis (data obtained from trial investigators)
Notes	41 infants left the study after randomisation for various reasons (insufficient maternal milk supply, death, reduced enteral intake for > 72 hours, incomplete data). Data for these infants were not included in intention-to-treat analyses of growth outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded

Pettifor 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	41 (of 100) infants left the study after randomisation for various reasons (insufficient maternal milk supply, death, reduced enteral intake for > 72 hours, incomplete data) . These infants were not included in intention-to-treat analyses of growth outcomes

Polberger 1989

Methods	Randomised controlled trial
Participants	34 VLBW infants Eligibility criteria: birth weight appropriate for gestational age, tolerance of complete enteral feeding (170 mL/kg/d), no obvious disease or major malformations, no supplemental oxygen therapy Setting: 2 neonatal units in Lund and Malmö, Sweden
Interventions	Intervention (N = 7): maternal or donor milk supplemented with (per 100 mL) 1.0 g human milk protein and 1.0 g human milk fat Control 1 (N = 7): maternal or donor milk with no fortification Feeds of 170 mL/kg/d were given throughout the study. When mother's own milk was insufficient, mature human milk from a milk bank was used. All infants, regardless of group allocation, received enteral supplementation with vitamin E, folic acid, a multivitamin preparation and additional vitamin D. They also received one-off administration of calcium and phosphate, and from 4 weeks of age, elemental iron was given
Outcomes	• Growth parameters
Notes	Six infants left the study after randomisation for various reasons (apnoea, intolerance to the fixed feed volume, need for intravenous therapy). These infants were not included in intention-to-treat analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Report states that "closed envelopes" were used, but it is not specified whether these were sequentially numbered, opaque and sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is described as "double-blind", but it was not specified who was blinded

Polberger 1989 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is described as "double-blind", but it was not specified who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Several (up to 6, but exact number unclear) infants were excluded from the study after randomisation. Intention-to-treat analyses were not reported

Porcelli 1992

Methods	Randomised controlled trial
Participants	20 preterm infants with birth weight between 1110 and 2000 g Eligibility criteria: none reported Setting: Pediatric Hospital "V. Buzzi", Milano, Italy
Interventions	Intervention (N = 10): human milk fortified with FM85 Nestlè (including energy and protein) Control 1 (N =10): human milk with no fortification All infants received supplemental vitamin D
Outcomes	• Growth parameters • Metabolic parameters • Measures of bone mineralisation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomized", but method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment were not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Wauben 1998

Methods	Randomised controlled trial
Participants	31 preterm infants of birth weight < 1800 g Eligibility criteria: older than 1 week of age (birth weight appropriate for gestational age), consumption of full oral feeds (enteral intake 160 mL/kg/d) for longer than 5 days, stable weight gain greater than 10 g/kg/d, no severe congenital malformations/chromosomal abnormalities, no gastrointestinal disease Setting: Neonatal Units of the Children's Hospitals of the Hamilton Health Sciences Corporation and St Joseph's Hospitals, Hamilton, Ontario, Canada
Interventions	Intervention (N = 15): maternal milk fortified with (per 100 mL) 0.37 g human milk protein, 3.47 g carbohydrate, 61 mg calcium, 44 mg phosphorus, electrolytes and other minerals and vitamins (including vitamin D 472 IU/d) (Wyeth-Ayerst, Toronto, Ontario, Canada) (fortification commenced when maternal milk contributed > 80% of infant's enteral intake) Control (N = 16): maternal milk supplemented with calcium glycerophosphate
Outcomes	• Short-term growth • Biochemical indices of bone metabolism • Bone mineral content
Notes	Supplementation in both groups was increased gradually until a target amount was reached. Intervention ceased at discharge or at 38 weeks' postmenstrual age, whichever occurred later Infants in the control arm were significantly lighter at birth and were significantly lighter and shorter at study entry than infants in the group receiving HMF Nutrient intakes were measured: mean fluid intakes significantly greater in the control group (177 vs 164 mL/kg/d)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment were not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Six infants (3 in each group) were excluded from the study after randomisation. Details were reported, and no bias was apparent between groups. Intention-to-treat analyses

Wauben 1998 (*Continued*)

		of growth outcomes data were not reported

Zuckerman 1994

Methods	Quasi-randomised controlled trial
Participants	56 infants with birth weight < 1200 g, older than 2 weeks of age Eligibility criteria: no congenital abnormalities, infections, nor disorders causing bone disease Setting: Baragwanath Hospital, Bertsham, South Africa
Interventions	Intervention (N = 29): maternal milk mixed in equal proportions with premature infant formula (Alprem, Nestle) to yield supplements (per 100 mL) of fat, carbohydrate and calcium 14.5 mg, phosphate 7 mg and protein 0.6 g Control (N = 27): unsupplemented human milk
Outcomes	• In-hospital growth rates • Serum indices of bone metabolism • Radiographic changes of metabolic bone disease
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Infants were assigned to the 2 groups according to their hospital number (odd or even)
Allocation concealment (selection bias)	High risk	Infants were assigned to the 2 groups according to their hospital number (odd or even)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded (radiographers were reported to have been blinded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three infants in the control group were excluded because of incorrect feeding

ALP - alkaline phosphatase
DEXA - dual-energy x-ray absorptiometry
NEC - necrotising enterocolitis
NICU - neonatal intensive care unit

VLBW - very low birth weight

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

Study	Reason for exclusion
Abrams 2014	Comparison of human milk-based vs cow's milk-based protein fortification
Arslanoglu 2009	Comparison of different fortification regimens, with no control group receiving unfortified milk
Carey 1987	Fortification with protein only; no fortification with energy
Greer 1988	Fortification with protein only; no fortification with energy
Hair 2014	Control group received fortified milk
Kashyap 1990	Fortification with protein only; no fortification with energy
Reali 2010	Literature review
Tarcan 2004	Not a randomised controlled trial

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

Mills 2015

Trial name or title	PREterM FOrmula Or Donor Breast Milk for Premature Babies (PREMFOOD)
Methods	Open, 3-arm randomised controlled feasibility trial
Participants	Neonates at < 30 weeks' gestation; babies with conditions that preclude enteral feeding or are immediately life-limiting are ineligible
Interventions	Participants will be randomised to receive fortified donor breast milk (DBM), unfortified DBM or preterm formula to make up any shortfall in maternal breast milk until 35 weeks' postmenstrual age, with a sample size of 22 in each group
Outcomes	Primary outcome measure: total body adiposity (measured as close as possible to the baby's due date, at an average age of 10 weeks (range 8 to 15 weeks))
Starting date	2015
Contact information	Prof. Neena Modi, Section of Neonatal Medicine, Imperial College London, London, UK; Department of Neonatal Medicine, Chelsea and Westminster Hospital, London, UK
Notes	Feasibility trial

DATA AND ANALYSES

Comparison 1. Fortified breast milk versus unfortified breast milk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight gain (g/kg/d)	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 All trials	10	635	Mean Difference (IV, Fixed, 95% CI)	1.81 [1.23, 2.40]
1.2 Trials recruiting only very preterm or VLBW infants	5	269	Mean Difference (IV, Fixed, 95% CI)	2.82 [1.83, 3.80]
1.3 Trials conducted in low- or middle-income countries	2	214	Mean Difference (IV, Fixed, 95% CI)	1.86 [0.70, 3.01]
2 Length gain (cm/wk)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 All trials	8	555	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.07, 0.17]
2.2 Trials recruiting only very preterm or VLBW infants	3	189	Mean Difference (IV, Fixed, 95% CI)	0.21 [0.14, 0.28]
2.3 Trials conducted in low- or middle-income countries	1	157	Mean Difference (IV, Fixed, 95% CI)	0.18 [0.10, 0.26]
3 Head growth (cm/wk)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 All trials	8	555	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.04, 0.12]
3.2 Trials recruiting only very preterm or VLBW infants	3	189	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.05, 0.17]
3.3 Trials conducted in low- or middle-income countries	1	157	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.02, 0.14]
4 Weight at 12 to 18 months (kg)	2	270	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.31, 0.25]
5 Length at 12 to 18 months (cm)	2	270	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.98, 0.60]
6 Head circumference at 12 to 18 months (cm)	2	270	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.37, 0.18]
7 Mental development index at 18 months	1	245	Mean Difference (IV, Fixed, 95% CI)	2.20 [-3.35, 7.75]
8 Psychomotor development index at 18 months	1	245	Mean Difference (IV, Fixed, 95% CI)	2.40 [-1.90, 6.70]
9 Length of hospital stay (weeks)	2	210	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.16, 0.93]
9.1 All trials	2	210	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.16, 0.93]
10 Feed intolerance	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 All trials	5	255	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.49]
10.2 Trials recruiting only very preterm or VLBW infants	2	174	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.22]
10.3 Trials conducted in low- or middle-income countries	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.23]
11 Necrotising enterocolitis	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 All trials	11	882	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.76, 3.23]
11.2 Trials recruiting only very preterm or VLBW infants	7	539	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.49, 2.88]
11.3 Trials conducted in low- or middle-income countries	3	310	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.33, 9.11]

12 Serum ALP (IU/L): restricted to trials without mineral supplementation of the control group	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 All trials	5	325	Mean Difference (IV, Fixed, 95% CI)	-126.36 [-190.89, -61.83]
12.2 Trials recruiting only very preterm or VLBW infants	4	265	Mean Difference (IV, Fixed, 95% CI)	-132.03 [-198.09, -65.98]
12.3 Trials conducted in low- or middle-income countries	4	309	Mean Difference (IV, Fixed, 95% CI)	-119.66 [-185.54, -53.78]
13 Bone mineral content (mg/cm): restricted to trials without mineral supplementation of the control group	1	59	Mean Difference (IV, Fixed, 95% CI)	12.00 [6.28, 17.72]

Analysis 1.1. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 1 Weight gain (g/kg/d).

Review: Multi-nutrient fortification of human milk for preterm infants

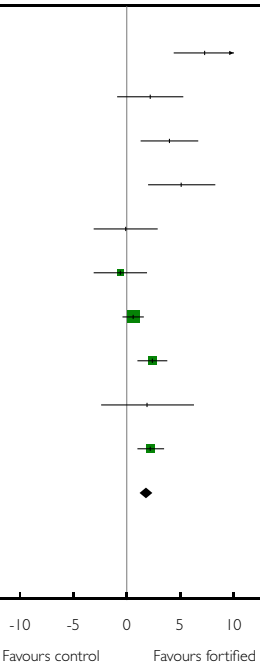
Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 1 Weight gain (g/kg/d)

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 All trials							
Modanlou 1986	8	26.7 (3.4)	10	19.4 (2.7)		4.0 %	7.30 [4.41, 10.19]
Gross 1987 (1)	10	19.9 (2.5)	10	17.7 (4.4)		3.4 %	2.20 [-0.94, 5.34]
Gross 1987 (2)	17	21.5 (3.5)	9	17.5 (3.3)		4.6 %	4.00 [1.28, 6.72]
Polberger 1989	7	20.4 (2.8)	7	15.3 (3.2)		3.4 %	5.10 [1.95, 8.25]
Pettifor 1989	29	16.7 (5)	28	16.8 (6.4)		3.8 %	-0.10 [-3.09, 2.89]
Porcelli 1992	10	11.4 (2.7)	10	12 (3)		5.4 %	-0.60 [-3.10, 1.90]
Lucas 1996	137	15.6 (4.7)	138	15 (3.5)		35.2 %	0.60 [-0.38, 1.58]
Wauben 1998	12	16.6 (1.6)	13	14.2 (2)		16.9 %	2.40 [0.99, 3.81]
Nicholl 1999	13	15.1 (3.3)	10	13.2 (6.4)		1.8 %	1.90 [-2.45, 6.25]
Mukhopadhyay 2007	82	15.1 (4)	75	12.9 (4)		21.5 %	2.20 [0.95, 3.45]
Subtotal (95% CI)	**325**		**310**			**100.0 %**	**1.81 [1.23, 2.40]**

Heterogeneity: Chi^2 = 32.63, df = 9 (P = 0.00015); I^2 =72%

Test for overall effect: Z = 6.12 (P < 0.00001)



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Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 Trials recruiting only very preterm or VLBW infants							
Modanlou 1986	8	26.7 (3.4)	10	19.4 (2.7)		11.7 %	7.30 [4.41, 10.19]
Pettifor 1989	29	16.7 (5)	28	16.8 (6.4)		10.9 %	-0.10 [-3.09, 2.89]
Polberger 1989	7	20.4 (2.8)	7	15.3 (3.2)		9.9 %	5.10 [1.95, 8.25]
Nicholl 1999	13	15.1 (3.3)	10	13.2 (6.4)		5.2 %	1.90 [-2.45, 6.25]
Mukhopadhyay 2007	82	15.1 (4)	75	12.9 (4)		62.3 %	2.20 [0.95, 3.45]
Subtotal (95% CI)	**139**		**130**			**100.0 %**	**2.82 [1.83, 3.80]**
Heterogeneity: Chi^2 = 16.02, df = 4 (P = 0.003); I^2 =75%							
Test for overall effect: Z = 5.58 (P < 0.00001)							
3 Trials conducted in low- or middle-income countries							
Pettifor 1989	29	16.7 (5)	28	16.8 (6.4)		14.9 %	-0.10 [-3.09, 2.89]
Mukhopadhyay 2007	82	15.1 (4)	75	12.9 (4)		85.1 %	2.20 [0.95, 3.45]
Subtotal (95% CI)	**111**		**103**			**100.0 %**	**1.86 [0.70, 3.01]**
Heterogeneity: Chi^2 = 1.94, df = 1 (P = 0.16); I^2 =48%							
Test for overall effect: Z = 3.15 (P = 0.0016)							
Test for subgroup differences: Chi^2 = 3.04, df = 2 (P = 0.22), I^2 =34%							

Analysis 1.2. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 2 Length gain (cm/wk).

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 2 Length gain (cm/wk)

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 All trials							
Modanlou 1986	8	0.99 (0.4)	10	0.81 (0.44)		1.6 %	0.18 [-0.21, 0.57]
Gross 1987 (1)	10	0.89 (0.19)	10	0.81 (0.22)		7.3 %	0.08 [-0.10, 0.26]
Gross 1987 (2)	17	0.84 (0.25)	9	0.79 (0.12)		11.8 %	0.05 [-0.09, 0.19]
Polberger 1989	7	1.2 (0.17)	7	0.83 (0.17)		7.5 %	0.37 [0.19, 0.55]
Porcelli 1992	10	0.6 (0.2)	10	0.7 (0.3)		4.8 %	-0.10 [-0.32, 0.12]
Lucas 1996	137	0.93 (0.47)	138	0.96 (0.47)		19.3 %	-0.03 [-0.14, 0.08]
Wauben 1998	12	1.1 (0.2)	13	0.9 (0.2)		9.7 %	0.20 [0.04, 0.36]
Mukhopadhyay 2007	82	1.04 (0.3)	75	0.86 (0.2)		38.0 %	0.18 [0.10, 0.26]
Subtotal (95% CI)	**283**		**272**			**100.0 %**	**0.12 [0.07, 0.17]**
Heterogeneity: Chi^2 = 22.71, df = 7 (P = 0.002); I^2 =69%							
Test for overall effect: Z = 4.80 (P < 0.00001)							
2 Trials recruiting only very preterm or VLBW infants							
Modanlou 1986	8	0.99 (0.4)	10	0.81 (0.44)		3.3 %	0.18 [-0.21, 0.57]
Polberger 1989	7	1.2 (0.17)	7	0.83 (0.17)		15.9 %	0.37 [0.19, 0.55]
Mukhopadhyay 2007	82	1.04 (0.3)	75	0.86 (0.2)		80.7 %	0.18 [0.10, 0.26]
Subtotal (95% CI)	**97**		**92**			**100.0 %**	**0.21 [0.14, 0.28]**
Heterogeneity: Chi^2 = 3.67, df = 2 (P = 0.16); I^2 =46%							
Test for overall effect: Z = 5.80 (P < 0.00001)							
3 Trials conducted in low- or middle-income countries							
Mukhopadhyay 2007	82	1.04 (0.3)	75	0.86 (0.2)		100.0 %	0.18 [0.10, 0.26]
Subtotal (95% CI)	**82**		**75**			**100.0 %**	**0.18 [0.10, 0.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.46 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 4.72, df = 2 (P = 0.09), I^2 =58%							

Analysis 1.3. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 3 Head growth (cm/wk).

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 3 Head growth (cm/wk)

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 All trials							
Modanlou 1986	8	1.09 (0.07)	10	0.82 (0.24)		6.2 %	0.27 [0.11, 0.43]
Gross 1987 (1)	10	0.92 (0.09)	10	0.83 (0.16)		11.7 %	0.09 [-0.02, 0.20]
Gross 1987 (2)	17	0.84 (0.21)	9	0.84 (0.09)		11.3 %	0.0 [-0.12, 0.12]
Polberger 1989	7	1.11 (0.13)	7	0.94 (0.25)		3.5 %	0.17 [-0.04, 0.38]
Porcelli 1992	10	0.7 (0.3)	10	0.7 (0.2)		3.0 %	0.0 [-0.22, 0.22]
Lucas 1996	137	1.01 (0.47)	138	0.95 (0.35)		15.7 %	0.06 [-0.04, 0.16]
Wauben 1998	12	1 (0.1)	13	0.9 (0.2)		10.1 %	0.10 [-0.02, 0.22]
Mukhopadhyay 2007	82	0.83 (0.2)	75	0.75 (0.2)		38.6 %	0.08 [0.02, 0.14]
Subtotal (95% CI)	**283**		**272**			**100.0 %**	**0.08 [0.04, 0.12]**
Heterogeneity: Chi^2 = 8.96, df = 7 (P = 0.26); I^2 =22%							
Test for overall effect: Z = 4.21 (P = 0.000026)							
2 Trials recruiting only very preterm or VLBW infants							
Modanlou 1986	8	1.09 (0.07)	10	0.82 (0.24)		12.8 %	0.27 [0.11, 0.43]
Polberger 1989	7	1.11 (0.13)	7	0.94 (0.25)		7.2 %	0.17 [-0.04, 0.38]
Mukhopadhyay 2007	82	0.83 (0.2)	75	0.75 (0.2)		80.0 %	0.08 [0.02, 0.14]
Subtotal (95% CI)	**97**		**92**			**100.0 %**	**0.11 [0.05, 0.17]**
Heterogeneity: Chi^2 = 5.22, df = 2 (P = 0.07); I^2 =62%							
Test for overall effect: Z = 3.88 (P = 0.00011)							
3 Trials conducted in low- or middle-income countries							
Mukhopadhyay 2007	82	0.83 (0.2)	75	0.75 (0.2)		100.0 %	0.08 [0.02, 0.14]
Subtotal (95% CI)	**82**		**75**			**100.0 %**	**0.08 [0.02, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.50 (P = 0.012)							
Test for subgroup differences: Chi^2 = 0.74, df = 2 (P = 0.69), I^2 =0.0%							

Analysis 1.4. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 4 Weight at 12 to 18 months (kg).

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 4 Weight at 12 to 18 months (kg)

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lucas 1996	125	10.05 (1.34)	120	10.09 (1.1)		84.2 %	-0.04 [-0.35, 0.27]
Wauben 1998	12	9 (0.9)	13	9 (0.9)		15.8 %	0.0 [-0.71, 0.71]
Total (95% CI)	**137**		**133**			**100.0 %**	**-0.03 [-0.31, 0.25]**

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 0.23 (P = 0.81)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 5 Length at 12 to 18 months (cm).

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 5 Length at 12 to 18 months (cm)

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lucas 1996	125	80 (3.35)	120	80.1 (3.29)		90.0 %	-0.10 [-0.93, 0.73]
Wauben 1998	12	74.9 (3.7)	13	75.9 (2.5)		10.0 %	-1.00 [-3.50, 1.50]
Total (95% CI)	**137**		**133**			**100.0 %**	**-0.19 [-0.98, 0.60]**

Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 6 Head circumference at 12 to 18 months (cm).

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

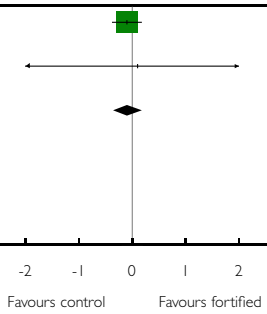
Outcome: 6 Head circumference at 12 to 18 months (cm)

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lucas 1996	125	48 (1.12)	120	48.1 (1.1)		98.6 %	-0.10 [-0.38, 0.18]
Wauben 1998	12	46.9 (3.9)	13	46.8 (1.3)		1.4 %	0.10 [-2.22, 2.42]
Total (95% CI)	**137**		**133**			**100.0 %**	**-0.10 [-0.37, 0.18]**

Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable

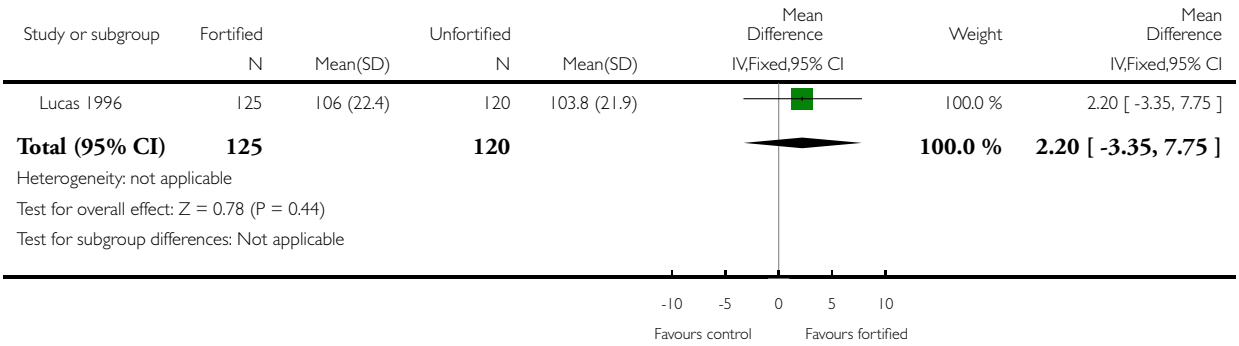


Analysis 1.7. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 7 Mental development index at 18 months.

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 7 Mental development index at 18 months

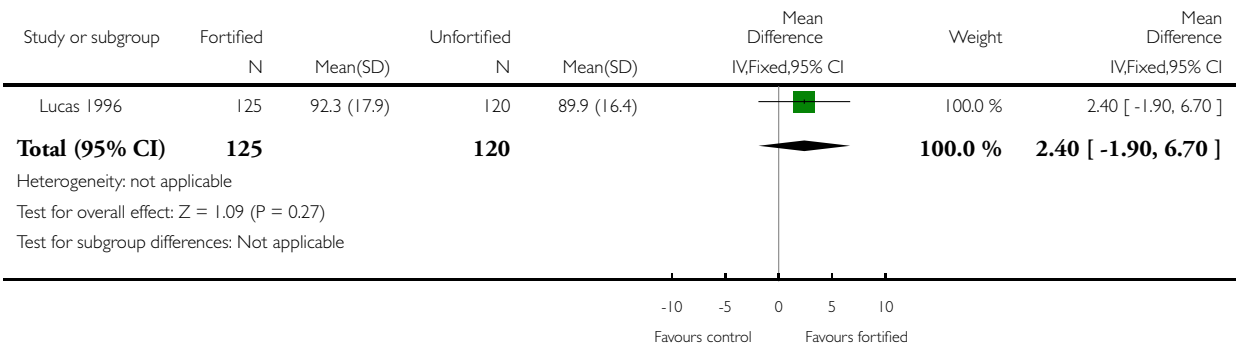


Analysis 1.8. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 8 Psychomotor development index at 18 months.

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 8 Psychomotor development index at 18 months

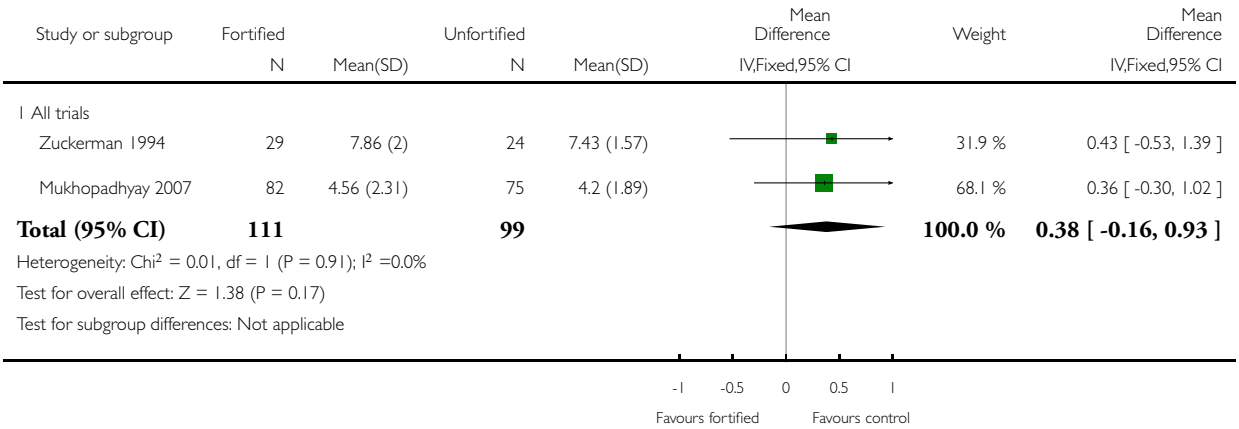


Analysis 1.9. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 9 Length of hospital stay (weeks).

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 9 Length of hospital stay (weeks)

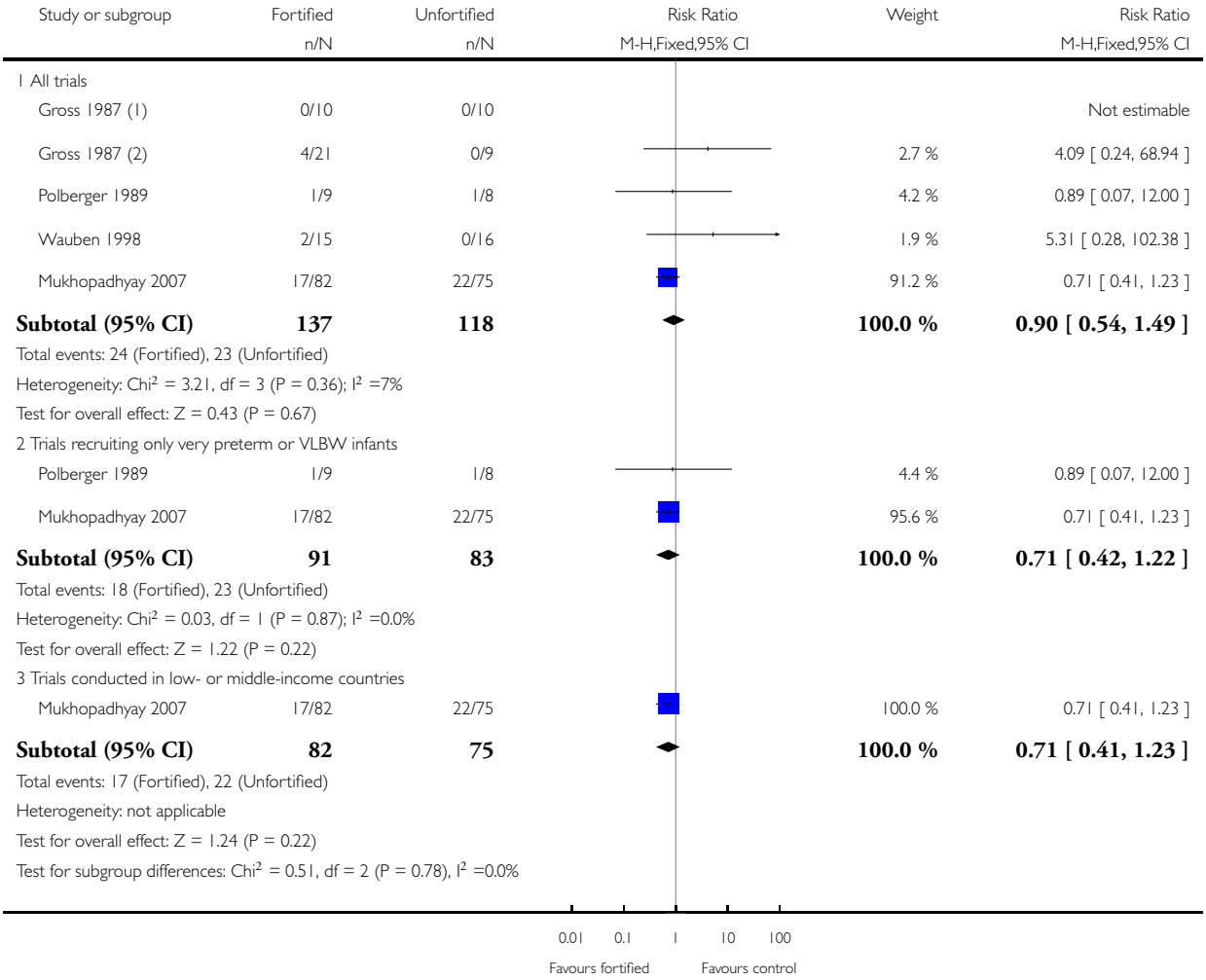


Analysis 1.10. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 10 Feed intolerance.

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 10 Feed intolerance

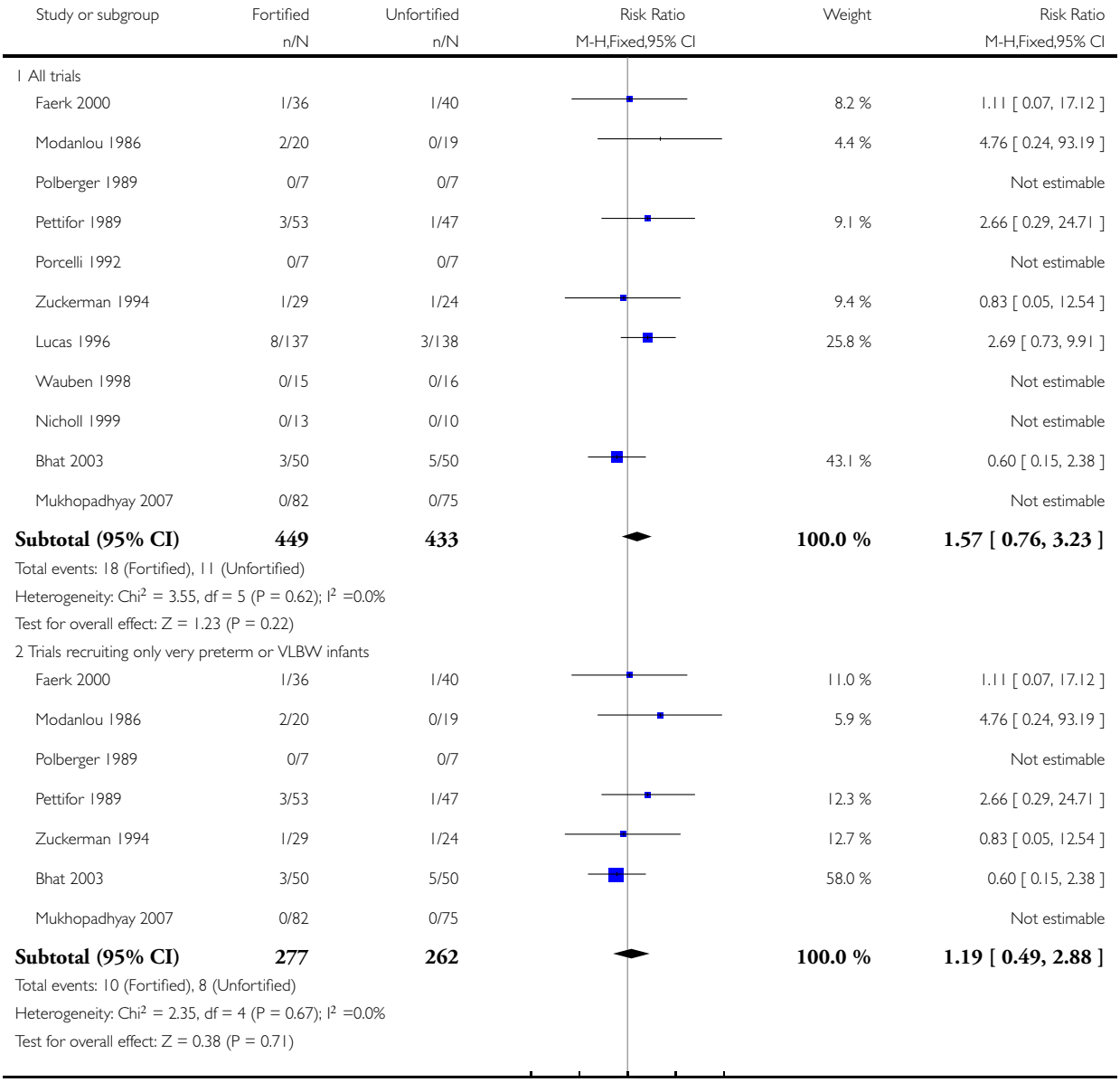


Analysis 1.11. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 11 Necrotising enterocolitis.

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 11 Necrotising enterocolitis



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Study or subgroup	Fortified n/N	Unfortified n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Trials conducted in low- or middle-income countries					
Pettifor 1989	3/53	1/47		49.2 %	2.66 [0.29, 24.71]
Zuckerman 1994	1/29	1/24		50.8 %	0.83 [0.05, 12.54]
Mukhopadhyay 2007	0/82	0/75			Not estimable
Subtotal (95% CI)	**164**	**146**		**100.0 %**	**1.73 [0.33, 9.11]**
Total events: 4 (Fortified), 2 (Unfortified)					
Heterogeneity: Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: Chi^2 = 0.29, df = 2 (P = 0.87), I^2 =0.0%					

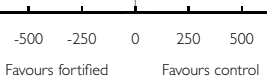
Analysis 1.12. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 12 Serum ALP (IU/L): restricted to trials without mineral supplementation of the control group.

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

Outcome: 12 Serum ALP (IU/L): restricted to trials without mineral supplementation of the control group

Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 All trials							
Gathwala 2012	30	711 (646)	30	719 (542)		4.6 %	-8.00 [-309.75, 293.75]
Modanlou 1986	7	790 (202)	9	1075 (434)		4.1 %	-285.00 [-605.61, 35.61]
Mukhopadhyay 2007	82	556 (231)	75	636 (245)		74.7 %	-80.00 [-154.66, -5.34]
Pettifor 1989	29	483 (152)	30	843 (514)		11.3 %	-360.00 [-552.07, -167.93]
Zuckerman 1994	18	620 (368)	15	881 (435)		5.4 %	-261.00 [-539.14, 17.14]
Subtotal (95% CI)	**166**		**159**			**100.0 %**	**-126.36 [-190.89, -61.83]**
Heterogeneity: Chi^2 = 9.60, df = 4 (P = 0.05); I^2 =58%							



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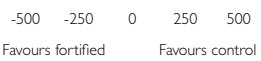
Study or subgroup	Fortified N	Mean(SD)	Unfortified N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 3.84 (P = 0.00012)							
2 Trials recruiting only very preterm or VLBW infants							
Modanlou 1986	7	790 (202)	9	1075 (434)		4.2 %	-285.00 [-605.61, 35.61]
Mukhopadhyay 2007	82	556 (231)	75	636 (245)		78.3 %	-80.00 [-154.66, -5.34]
Pettifor 1989	29	483 (152)	30	843 (514)		11.8 %	-360.00 [-552.07, -167.93]
Zuckerman 1994	18	620 (368)	15	881 (435)		5.6 %	-261.00 [-539.14, 17.14]
Subtotal (95% CI)	**136**		**129**			**100.0 %**	**-132.03 [-198.09, -65.98]**
Heterogeneity: Chi^2 = 8.98, df = 3 (P = 0.03); I^2 =67%							
Test for overall effect: Z = 3.92 (P = 0.000089)							
3 Trials conducted in low- or middle-income countries							
Gathwala 2012	30	711 (646)	30	719 (542)		4.8 %	-8.00 [-309.75, 293.75]
Mukhopadhyay 2007	82	556 (231)	75	636 (245)		77.9 %	-80.00 [-154.66, -5.34]
Pettifor 1989	29	483 (152)	30	843 (514)		11.8 %	-360.00 [-552.07, -167.93]
Zuckerman 1994	18	620 (368)	15	881 (435)		5.6 %	-261.00 [-539.14, 17.14]
Subtotal (95% CI)	**159**		**150**			**100.0 %**	**-119.66 [-185.54, -53.78]**
Heterogeneity: Chi^2 = 8.62, df = 3 (P = 0.03); I^2 =65%							
Test for overall effect: Z = 3.56 (P = 0.00037)							
Test for subgroup differences: Chi^2 = 0.07, df = 2 (P = 0.97), I^2 =0.0%							



Analysis 1.13. Comparison 1 Fortified breast milk versus unfortified breast milk, Outcome 13 Bone mineral content (mg/cm): restricted to trials without mineral supplementation of the control group.

Review: Multi-nutrient fortification of human milk for preterm infants

Comparison: 1 Fortified breast milk versus unfortified breast milk

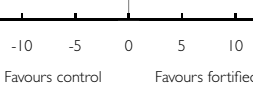
Outcome: 13 Bone mineral content (mg/cm): restricted to trials without mineral supplementation of the control group

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pettifor 1989	29	59 (13)	30	47 (9)		100.0 %	12.00 [6.28, 17.72]
Total (95% CI)	**29**		**30**			**100.0 %**	**12.00 [6.28, 17.72]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.11 (P = 0.000040)

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy

An updated de-duplicated search of MEDLINE via PubMed, EMBASE, CINAHL and *The Cochrane Library (2016, Issue 2)*
Searched 29/02/16, using the search terms below, yielded 93 new articles.
MEDLINE and MEDLINE In-Process
Searched 09/12/14 via OVID interface.
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 exp Infant, Newborn/ (513323)
2 Premature Birth/ (7404)
3 (neonat$ or neo nat$).ti,ab. (205534)
4 (newborn$ or new born$ or newly born$).ti,ab. (136536)
5 (preterm or preterms or pre term or pre terms).ti,ab. (50338)
6 (preemie$ or premie or premies).ti,ab. (118)
7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (12271)
8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (26861)
9 (lbw or vlbw or elbw).ti,ab. (5920)
10 infan$.ti,ab. (348181)
11 (baby or babies).ti,ab. (54731)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (862662)
13 Milk, Human/ (16063)
14 Food, Fortified/ (7944)
15 13 and 14 (396)

16 ((fortif$ or supplemented or supplementation) adj4 ((human or breast or expressed) adj2 milk)).ti,ab. (566)
17 15 or 16 (781)
18 12 and 17 (730)

EMBASE
Searched 09/12/14 via OVID interface.
Database: Embase <1974 to 2014 Week 49>
Search Strategy:
1 exp newborn/ (475396)
2 prematurity/ (74237)
3 (neonat$ or neo nat$).ti,ab. (245289)
4 (newborn$ or new born$ or newly born$).ti,ab. (158274)
5 (preterm or preterms or pre term or pre terms).ti,ab. (62693)
6 (preemie$ or premie or premies).ti,ab. (159)
7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (15319)
8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (30730)
9 (lbw or vlbw or elbw).ti,ab. (7192)
10 infan$.ti,ab. (394252)
11 (baby or babies).ti,ab. (69392)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (929097)
13 breast milk/ (20455)
14 diet supplementation/ (65275)
15 13 and 14 (863)
16 ((fortif$ or supplemented or supplementation) adj4 ((human or breast or expressed) adj2 milk)).ti,ab. (677)
17 15 or 16 (1404)
18 12 and 17 (1194)

CINAHL Plus
Searched 09/12/14 via EBSCO interface, Search modes - Boolean/Phrase.
Search Strategy:
S17 S11 AND S16 (222)
S16 S14 OR S15 (243)
S15 TI (((fortif* or supplemented or supplementation) N4 ((human or breast or expressed) N2 milk))) OR AB (((fortif* or supplemented or supplementation) N4 ((human or breast or expressed) N2 milk))) (153)
S14 S12 AND S13 (141)
S13 (MH "Food, Fortified") (2,431)
S12 (MH "Milk, Human") (3,457)
S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 (139,268)
S10 TI ((baby or babies)) OR AB ((baby or babies)) (17,329)
S9 TI infan* OR AB infan* (54,724)
S8 TI ((lbw or vlbw or elbw)) OR AB ((lbw or vlbw or elbw)) (1,486)
S7 TI ((low N3 (birthweight* or birth weight*))) OR AB ((low N3 (birthweight* or birth weight*))) (6,186)
S6 TI ((prematur* N3 (birth* or born or deliver*))) OR AB ((prematur* N3 (birth* or born or deliver*))) (2,040)
S5 TI ((preemie* or premie or premies)) OR AB ((preemie* or premie or premies)) (194)
S4 TI ((preterm or preterms or pre term or pre terms)) OR AB ((preterm or preterms or pre term or pre terms)) (14,213)
S3 TI ((newborn* or new born* or newly born*)) OR AB ((newborn* or new born* or newly born*)) (14,806)
S2 TI ((neonat* or neo nat*)) OR AB ((neonat* or neo nat*)) (29,882)
S1 (MH "Infant, Newborn+") OR (MH "Infant, Premature") (86,648)

Maternity and Infant Care
Searched 09/12/14 via OVID interface.
Database: Maternity and Infant Care <1971 to October 2014>
Search Strategy:

1 ((fortif$ or supplemented or supplementation) adj4 ((human or breast or expressed) adj2 milk)).ti,ab. (221)

WHAT'S NEW

Last assessed as up-to-date: 29 February 2016.

Date	Event	Description
21 March 2016	New citation required and conclusions have changed	This review updates the review titled "Multicomponent fortified human milk for promoting growth in preterm infants" (Kuschel 2009)

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1998

Date	Event	Description
29 August 2003	New search has been performed	This review updates the existing review titled "Multicomponent fortified human milk for promoting growth in preterm infants", published in *The Cochrane Library*, Issue 4, 1998 This review presents 6 new studies (included - Zuckerman, Nicholl, Faerk; excluded - Gupta, Porcelli, Reiss) and 1 follow-up report (Wauben)

CONTRIBUTIONS OF AUTHORS

Jennifer Brown and William McGuire screened and appraised reports identified in the updated search, extracted and analysed data from included studies and drafted the review. Nick Embleton and Jane Harding arbitrated inclusion and data extraction disagreements and drafted the review.

DECLARATIONS OF INTEREST

None.

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We defined "multi-nutrient" fortifier as one that contains both protein and carbohydrate or fat (non-protein energy) with the option of including other nutrients, such as minerals, vitamins or electrolytes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Food, Fortified; *Infant Nutritional Physiological Phenomena; *Milk, Human [chemistry]; Infant, Premature [*growth & development]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn