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Early full enteral feeding for preterm or low birth weight infants (Review)

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Early full enteral feeding for preterm or low birth weight infants.
Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD013542.
DOI: 10.1002/14651858.CD013542.pub2.

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[Intervention Review]

Early full enteral feeding for preterm or low birth weight infants

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 12, 2020.

Citation: Walsh V, Brown JV, Copperthwaite BR, Oddie SJ, McGuire W. Early full enteral feeding for preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No.: CD013542. DOI: 10.1002/14651858.CD013542.pub2.

ABSTRACT

Background

The introduction and advancement of enteral feeds for preterm or low birth weight infants is often delayed because of concerns that early full enteral feeding will not be well tolerated or may increase the risk of necrotising enterocolitis. Early full enteral feeding, however, might increase nutrient intake and growth rates; accelerate intestinal physiological, metabolic, and microbiomic postnatal transition; and reduce the risk of complications associated with intravascular devices for fluid administration.

Objectives

To determine how early full enteral feeding, compared with delayed or progressive introduction of enteral feeds, affects growth and adverse events such as necrotising enterocolitis, in preterm or low birth weight infants.

Search methods

We used the standard search strategy of Cochrane Neonatal to search Cochrane Central Register of Controlled Trials; MEDLINE Ovid, Embase Ovid, Maternity & Infant Care Database Ovid, the Cumulative Index to Nursing and Allied Health Literature, and clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials to October 2020.

Selection criteria

Randomised controlled trials that compared early full enteral feeding with delayed or progressive introduction of enteral feeds in preterm or low birth weight infants.

Data collection and analysis

We used the standard methods of Cochrane Neonatal. Two review authors separately assessed trial eligibility, evaluated trial quality, extracted data, and synthesised effect estimates using risk ratios (RR), risk differences, and mean differences (MD) with 95% confidence intervals (CI). We used the GRADE approach to assess the certainty of evidence.

Main results

We included six trials. All were undertaken in the 2010s in neonatal care facilities in India. In total, 526 infants participated. Most were very preterm infants of birth weight between 1000 g and 1500 g. Trials were of good methodological quality, but a potential source of bias was that parents, clinicians, and investigators were not masked. The trials compared early full feeding (60 mL/kg to 80 mL/kg on day one after birth) with minimal enteral feeding (typically 20 mL/kg on day one) supplemented with intravenous fluids. Feed volumes were advanced daily as tolerated by 20 mL/kg to 30 mL/kg body weight to a target steady-state volume of 150 mL/kg to 180 mL/kg/day. All participating

infants were fed preferentially with maternal expressed breast milk, with two trials supplementing insufficient volumes with donor breast milk and four supplementing with preterm formula.

Few data were available to assess growth parameters. One trial (64 participants) reported a slower rate of weight gain (median difference –3.0 g/kg/day), and another (180 participants) reported a faster rate of weight gain in the early full enteral feeding group (MD 1.2 g/kg/day). We did not meta-analyse these data (very low-certainty evidence). None of the trials reported rate of head circumference growth. One trial reported that the mean z-score for weight at hospital discharge was higher in the early full enteral feeding group (MD 0.24, 95% CI 0.06 to 0.42; low-certainty evidence). Meta-analyses showed no evidence of an effect on necrotising enterocolitis (RR 0.98, 95% CI 0.38 to 2.54; 6 trials, 522 participants; I^2 = 51%; very low-certainty evidence).

Authors' conclusions

Trials provided insufficient data to determine with any certainty how early full enteral feeding, compared with delayed or progressive introduction of enteral feeds, affects growth in preterm or low birth weight infants. We are uncertain whether early full enteral feeding affects the risk of necrotising enterocolitis because of the risk of bias in the trials (due to lack of masking), inconsistency, and imprecision.

PLAIN LANGUAGE SUMMARY

Early full enteral feeds for preterm or low birth weight infants

Review question: do preterm or low birth weight infants (babies born early or small) grow faster and have fewer problems when they receive all their nutrients as milk feeds from shortly after birth (compared with gradually introducing milk feeds while giving fluid or nutrients via an intravenous drip (a slow infused into the bloodstream via a vein))?

Background: 'early full enteral feeding' means that preterm or low birth weight infants receive all their nutrition as milk feeds from shortly after birth, and do not receive any supplemental fluids or nutrition via intravenous drips. Assessing whether this approach is safe and beneficial is particularly relevant to feeding very preterm or very low birth weight infants (born before 32 weeks, or birth weigh less than 1500 g).

Study characteristics: we included six trials, all undertaken in neonatal care units in India during the 2010s. The trials were generally good quality although most were small (involving 526 infants in total). Participants were preterm infants of birth weight 1000 g to 1500 g.

The search is up to date as of July 2020.

Key results: there were insufficient data to show whether infants who received full milk feeds from birth put on weight and grew more quickly than those for whom feeds were introduced gradually during the first week or two after birth. The trials reported no information about the effects early full milk feeds might have on development and growth later in the baby's life. The included trials found no evidence of other potential benefits or harms of early full feeds, including any effects on feeding or bowel problems.

Conclusion: there is not enough evidence to determine whether early full milk feeds benefit preterm or low birth weight infants. New trials would be needed to resolve this uncertainty.

Quality of evidence: we assessed this evidence as being of low or very low quality because the included trials were small with some methodological weaknesses and their findings were inconsistent with each other. This means that further research is very likely to have an important impact on the estimates of effect and our confidence in the findings.

SUMMARY OF FINDINGS

Summary of findings 1. Early full enteral feeding compared to delayed or progressive feeding for preterm or low birth weight infants

Early full compared to delayed/progressive enteral feeding for preterm or low birth weight infants

Patient or population: preterm or low birth weight infants
Setting: neonatal care facilities (India)
Intervention: early full enteral feeding
Comparison: delayed/progressive enteral feeding

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with delayed/progressive enteral feeding	Risk difference with early full enteral feeding
In hospital rate of weight gain (g/kg/day) until term equivalent	236 (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b,c]	—	Meta-analysis not possible due to different outcome measures.	
In hospital rate of head circumference growth (cm/week) until term equivalent – not reported	—	—	—	—	—
Growth restriction (z-score of weight) at hospital discharge	46 (1 RCT)	⊕⊕⊖⊖ **Low** [a,d]	—	The mean growth restriction (z-score of weight) at hospital discharge was –1.09	Mean 0.24 higher (0.06 higher to 0.42 higher)
Necrotising enterocolitis	522 (6 RCTs)	⊕⊖⊖⊖ **Very low** [a,e,f]	**RR 0.98** (0.38 to 2.54)	**Study population**	
				31 per 1000	1 fewer per 1000 (19 fewer to 47 more)

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

[a]Downgraded one level due to risk of surveillance and detection bias owing to lack of masking.
[b]Downgraded one level due to wide range point estimates across the two trials (imprecision).
[c]Downgraded one level due to opposite direction of effect (inconsistency).
[d]Downgraded one level as analysis included data from one small trial (imprecision).
[e]Downgraded one level due to moderate heterogeneity (inconsistency).
[f]Downgraded one level due to wide 95% confidence interval (imprecision).

BACKGROUND

This Cochrane Review appraised and synthesised data from randomised controlled trials (RCTs) that compared early full enteral feeding with delayed or progressive introduction of enteral feeds (combined with parenteral fluids or nutrition) for preterm or low birth weight (LBW; less than 2500 g) infants.

Description of the condition

Preterm or LBW infants, especially very preterm or very low birth weight (VLBW; less than 1500 g) infants, have few nutrient reserves at birth and are subject to physiological and metabolic stresses that increase their nutrient needs. Recommendations on nutrient requirements for preterm or LBW infants assume that the optimal rate of postnatal growth should be similar to that of uncompromised fetuses of an equivalent gestational age (Agostoni 2010; Tsang 1993). Such levels of nutrient input and growth are rarely achieved and most very preterm or VLBW infants accumulate nutrient deficits during their initial hospital stay (Embleton 2001; Horbar 2015). By the time they are ready to go home, many of these infants are growth restricted compared to their term-born peers (Clark 2003; Dusick 2003). Growth deficits can persist through childhood and adolescence, and are associated with adverse neurodevelopmental, cognitive, and educational outcomes (Bracewell 2008; Cooke 2003; Doyle 2004; Farooqi 2006; Ford 2000; Hack 1991; Leppänen 2014).

Necrotising enterocolitis

Necrotising enterocolitis, a syndrome of acute intestinal necrosis of unknown aetiology, affects about 1 in 20 very preterm or VLBW infants (Gagliardi 2008; Holman 1997; Moro 2009). Infants who develop necrotising enterocolitis experience more infections, have lower levels of nutrient intake, grow more slowly, and have longer durations of intensive care and hospital stay than gestation-comparable infants who do not develop necrotising enterocolitis (Bisquera 2002; Guthrie 2003). The associated mortality rate is greater than 20% (Fitzgibbons 2009). Compared with their peers, infants who develop necrotising enterocolitis have a higher incidence of long-term neurological disability, which may be a consequence of infection and undernutrition during a critical period of brain development (Berrington 2012; Pike 2012; Rees 2007).

In addition to low gestational age at birth, the major risk factor for necrotising enterocolitis is intrauterine growth restriction, especially if it is associated with absent or reversed end diastolic flow velocities in Doppler studies of the fetal aorta or umbilical artery (Dorling 2005; Samuels 2017). Most very preterm or VLBW infants who develop necrotising enterocolitis have received enteral milk feeds (Ramani 2013). Feeding with artificial formula rather than human milk increases the risk of developing necrotising enterocolitis (Quigley 2019; Walsh 2019). However, the available data from RCTs do not provide evidence that delaying the introduction of progressive enteral feeds beyond four days after birth, or advancing feed volumes more slowly than 24 mL/kg/day, affects the risk of necrotising enterocolitis and associated morbidities or mortality in very preterm or VLBW infants (Morgan 2013; Morgan 2014; Oddie 2017).

Early enteral feeding strategies

Evidence exists that early enteral feeding strategies – particularly the timing of introduction and the rate of advancement of milk feeds – affect important outcomes in preterm or LBW infants, including nutrient intake, the risk of necrotising enterocolitis, and growth and development (Embleton 2013). Approaches to early enteral feeding vary by the gestational age and clinical condition of the infant (Hay 2008; Klingenberg 2012). Stable preterm infants born at or more than 32 weeks' gestation, or with a birth weight of 1500 g or greater, are generally treated similarly to well term infants; all fluid and nutrition is supplied enterally from birth, either orally or via an intragastric feeding tube. In contrast, newborn infants who are extremely preterm (born before 28 weeks' gestation), or of extremely low birth weight (ELBW; less than 1000 g) are commonly affected by respiratory distress, have delayed gastric emptying and inefficient intestinal motility, and are at high risk of developing necrotising enterocolitis. These infants tend to be supported with parenteral fluids and nutrition during the first few days after birth. Enteral milk feeds are then introduced in subnutritional volumes (trophic feeds) during the first week after birth, ideally as colostrum or expressed breast milk, and the volume of feeds is increased gradually over the next one to two weeks as the volume of parenteral nutrition is decreased.

There remains substantial variation in practice with regard to early enteral feeding strategies for those preterm infants born at gestations between approximately 28 and 32 weeks (or with birth weights between approximately 1000 g and 1500 g). This variation reflects ongoing uncertainty about whether these infants should be treated in the same way as those infants born at a later gestation (i.e. with full enteral feeds from birth), or more similarly to extremely preterm or ELBW infants (i.e. delayed introduction and gradual advancement of milk feeds while supporting nutritional needs with parenteral nutrition). In many high-income countries, policy and practice has tended to favour the conservative approach to introducing and advancing enteral feeds for these infants because of concerns that early full enteral feeding might increase the risk of feed intolerance, gastro-oesophageal reflux and aspiration of stomach contents, hypoglycaemia, and necrotising enterocolitis in very preterm or VLBW infants (de Waard 2018; Klingenberg 2012; Leaf 2013; Maas 2018). However, in low- and middle-income countries with fewer resources for neonatal care, practice is more pragmatic and tends to favour early introduction and advancement of enteral feeds (sometimes facilitated by 'kangaroo' mother care) for stable infants born at 28 weeks' gestation or greater, or with a birth weight of 1000 g or more (Conde-Agudelo 2016; Sankar 2008).

Description of the intervention

Early (sometimes termed 'immediate') full enteral feeding means that newborn infants receive all their prescribed nutrition as milk feeds (either human milk or formula) and do not receive any supplemental parenteral fluids or nutrition from birth (Nangia 2018). This approach for feeding preterm infants has been advocated since the earliest days of modern neonatology but has tended to be reserved for clinically stable preterm infants of gestational age at birth of more than approximately 32 weeks (Klingenberg 2012; Smallpeice 1964). In most neonatal care facilities, particularly in high-income countries, the more common practice is to introduce enteral milk feeds for very preterm or VLBW infants at low volume (trophic feeds or minimal enteral nutrition)

and to then advance the feed volume slowly during the next one to two weeks. During this time, infants receive most of their fluids and nutrition parenterally, usually in the form of commercially available solutions containing amino acids, glucose, minerals, vitamins, and fats (Klingenberg 2012).

There are potential disadvantages associated with conservative enteral feeding regimens (Flidel-Rimon 2004; Flidel-Rimon 2006). Because gastrointestinal hormone secretion and motility are stimulated by milk feeds, delaying full enteral feeding may diminish the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonisation (Embleton 2017). Intestinal dysmotility and dysbiosis might exacerbate feed intolerance and delay the establishment of enteral feeding independently of parenteral nutrition (Pammi 2017). Prolonging the duration of parenteral nutrition is associated with infectious and metabolic complications that increase mortality and morbidity, prolong hospital stay, and adversely affect growth and development (Embleton 2013). Due to cost and equipment implications, parenteral nutrition is less easily available in low- and middle-income countries. In high-income settings, earlier achievement of full enteral feeds and an associated reduction of length of hospital stay could be associated with considerable resource savings (Embleton 2014).

How the intervention might work

The aims of early full enteral feeding are to avoid the risks and costs associated with provision of parenteral nutrition and to accelerate gastrointestinal physiological, endocrine and metabolic maturity and so allow infants to attain nutrient intakes to optimise growth and development. Early full enteral feeding in this vulnerable population might reduce the risk of infection associated with intravascular devices used to deliver parenteral nutrition (Flidel-Rimon 2004). Early provision of breast milk might promote successful expression and lactation and help establish maternal breast milk feeding as the primary source of infant nutrition (Hay 2008; Senterre 2014). However, there is some concern that exclusive enteral nutrition might not be sufficient to maintain normal blood glucose levels during the early metabolic transition phase in very preterm or VLBW infants, particularly in growth-restricted infants with limited nutrient reserves at birth (Klingenberg 2012). Furthermore, any beneficial effects may be negated if early full enteral feeding increases the risk of feed intolerance or necrotising enterocolitis in very preterm or VLBW infants (Chauhan 2008; Samuels 2017).

Why it is important to do this review

This review focuses on the comparison of early full enteral feeding versus gradual introduction of progressive enteral feeding in combination with parenteral fluids. Other Cochrane Reviews have addressed the questions of whether delaying the introduction of any enteral milk feeding or restricting feed volumes to trophic levels (minimal enteral nutrition) affect the risk of necrotising enterocolitis in very preterm or VLBW infants (Morgan 2013; Morgan 2014). The findings of this review complement these other reviews of early enteral feeding strategies and might inform policy, practice, or research in this field (Chauhan 2008).

OBJECTIVES

To determine how early full enteral feeding, compared with delayed or progressive introduction of enteral feeds, affects growth and adverse events such as necrotising enterocolitis, in preterm or low birth weight infants.

Where data were available, we planned subgroup analyses of very preterm or VLBW infants (versus infants born after a longer gestation or with higher birth weight), infants 'small for gestational age' at birth (versus those 'appropriate for gestation'), infants fed with human milk only (versus formula-fed infants), and trials set in low- or middle-income countries (versus high-income countries) (see: Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs or quasi-RCTs, including cluster-RCTs.

Types of participants

We included infants born preterm (less than 37 weeks' gestation) or with LBW (less than 2500 g).

Types of interventions

Intervention

Full enteral feeds from birth without parenteral fluids or nutrition. Early full enteral feeding is defined as sufficient volumes of milk being fed orally or via an enteric feeding tube from soon after birth, without parenteral supplementation at any point.

Comparison

Any other feeding regimen, such as delayed initiation of full milk feeds and gradual advancement of feed volumes while receiving supplemental fluid or nutrients parenterally.

Types of outcome measures

Primary outcomes

1. In hospital rate of weight gain (g/kg/day) until term equivalent.
2. In hospital rate of head circumference growth (cm/week) until term equivalent.
3. Growth restriction: z-score and proportion of infants who remain below the 10th percentile for the index population distribution of weight at term equivalent.
4. Necrotising enterocolitis, confirmed at surgery or autopsy or diagnosed by at least two of the following clinical features (Kliegman 1987):
   a. abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen;
   b. abdominal distension with abdominal radiograph with gaseous distension or frothy appearance (or both) of bowel lumen;
   c. blood in stool;
   d. lethargy, hypotonia, or apnoea (or combination of these).

Secondary outcomes

1. Feed intolerance during the trial intervention period that results in cessation in enteral feeding for more than four hours.
2. Episodes of hypoglycaemia (investigator defined) requiring treatment with enteral supplement (including milk feed or buccal dextrose gel) or with intravenous fluids (including dextrose solution).
3. Invasive infection, as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, or from a normally sterile body space.
4. Duration of birth hospitalisation (days).
5. All-cause mortality up to 36 to 44 weeks' postmenstrual age and one-year post-term.
6. Growth parameters assessed beyond infancy: weight, height, or head circumference and proportion of infants who remain below the 10th percentile for the index population's distribution, and measures of body composition (lean/fat mass) and body mass index.
7. Severe neurodevelopmental disability, assessed beyond infancy until adulthood: non-ambulant cerebral palsy, developmental quotient more than two standard deviations (SD) below the population mean and blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring or unimproved by amplification).

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal.

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 10) in the Cochrane Library; MEDLINE Ovid (1946 to October 2020), Embase Ovid (1974 to October 2020), Maternity & Infant Care Database Ovid (1971 to October 2020), and the Cumulative Index to Nursing and Allied Health Literature EBSCO (1982 to October 2020), using terms described in Appendix 1. We limited the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We applied no language restrictions.

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

Searching other resources

We examined the reference lists of studies identified as potentially relevant. We searched the abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2019), the European Society for Paediatric Research (1995 to 2020), the UK Royal College of Paediatrics and Child Health (2000 to 2019), and the Perinatal Society of Australia and New Zealand (2000 to 2019). 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 (see Dealing with missing data for further details).

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

Two review authors (JB, BC, or VW) independently screened the titles and abstracts of all studies and assess the full articles of all potentially relevant trials. We excluded studies that did not meet all the inclusion criteria and stated the reasons for exclusion in the Characteristics of excluded studies table. We discussed any disagreements until consensus was achieved.

Data extraction and management

Two review authors (JB, BC, or VW) used a form to independently extract data on design, methodology, participants, interventions, outcomes, and treatment effects from each included study. We discussed any disagreements until we reached a consensus. The data extraction form was based on forms used previously by the author team, with adaptations made to meet the requirements of this review.

Assessment of risk of bias in included studies

Two review authors (JB, BC, or VW) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017) for the following domains:

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective reporting (reporting bias);
7. any other bias.

We resolved any disagreements by discussion. We did not exclude trials on the basis of risk of bias, but planned to conduct sensitivity analyses, if applicable, to explore the consequences of synthesising evidence of variable quality.

See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We analysed the treatment effects in the individual trials and reported the risk ratio (RR) and risk difference (RD) for dichotomous data and the mean difference (MD) for continuous data, with 95% confidence intervals (CI). We planned to report number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis used was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster-randomised trials.

For cluster-randomised trials, we planned to undertake analyses at the level of the individual while accounting for clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Dealing with missing data

Where data were missing without explanation, and could not be derived, we used the following approaches.

1. Where we had concerns about the extent of missing data or potential bias in missing data, we contacted the original study investigators to request the missing data for primary outcomes only, for studies published within the past 10 years where an email address was easily available from the published papers.
2. Where possible, we planned to impute missing SD using the coefficient of variation, or calculate this from other available statistics including standard errors, CIs, t values, and P values.
3. If the data were assumed to be missing at random, we planned to analyse the data without imputing any missing values.
4. If data could not be assumed to be missing at random, we planned to impute the missing outcomes with replacement values, assuming all to have a poor outcome, and conduct sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

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

We examined the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and described the percentage of variability in effect estimates that may have been due to heterogeneity rather than to sampling error. If high levels of heterogeneity were detected (an I^2 value greater than 75%), we explored the possible sources (e.g. differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

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

Data synthesis

We used the fixed-effect model in Review Manager 5 for meta-analyses (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for the primary outcomes.

1. Trials in which infants received human milk only (maternal expressed milk or donor human milk) versus those where formula could be given instead of, or as a supplement to, human milk.
2. Very preterm infants (born at less than 32 weeks' gestation) versus infants born at 32 weeks' gestation or greater.
3. Very low birth weight infants (less than 1500 g) versus infants with a birth weight of 1500 g or greater.
4. Infants with a birth weight below the 10th percentile for the reference population ('small for gestation') versus infants with a birth weight at or above the 10th percentile ('appropriate for gestation').
5. Trials set in low- or middle-income countries versus trials set in high-income countries (for classification, see datahelpdesk.worldbank.org/knowledgebase/articles/906519#High_income (accessed 18 April 2019)).

Sensitivity analysis

We planned sensitivity analyses to determine if the findings were affected by including only studies of adequate methodology (low risk of bias), defined as those studies with adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up assessment of the trial primary outcome.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence of the following primary outcomes: in hospital rate of weight gain (g/kg/day) until term equivalent; in hospital rate of head circumference growth (cm/week) until term equivalent; growth restriction (z score of weight) at hospital discharge; necrotising enterocolitis.

Two review authors (VW and WM) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used GRADEpro GDT to create Summary of findings 1 to report the certainty of the evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

1. High certainty: further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low certainty: we are very uncertain about the estimate.

RESULTS

Description of studies

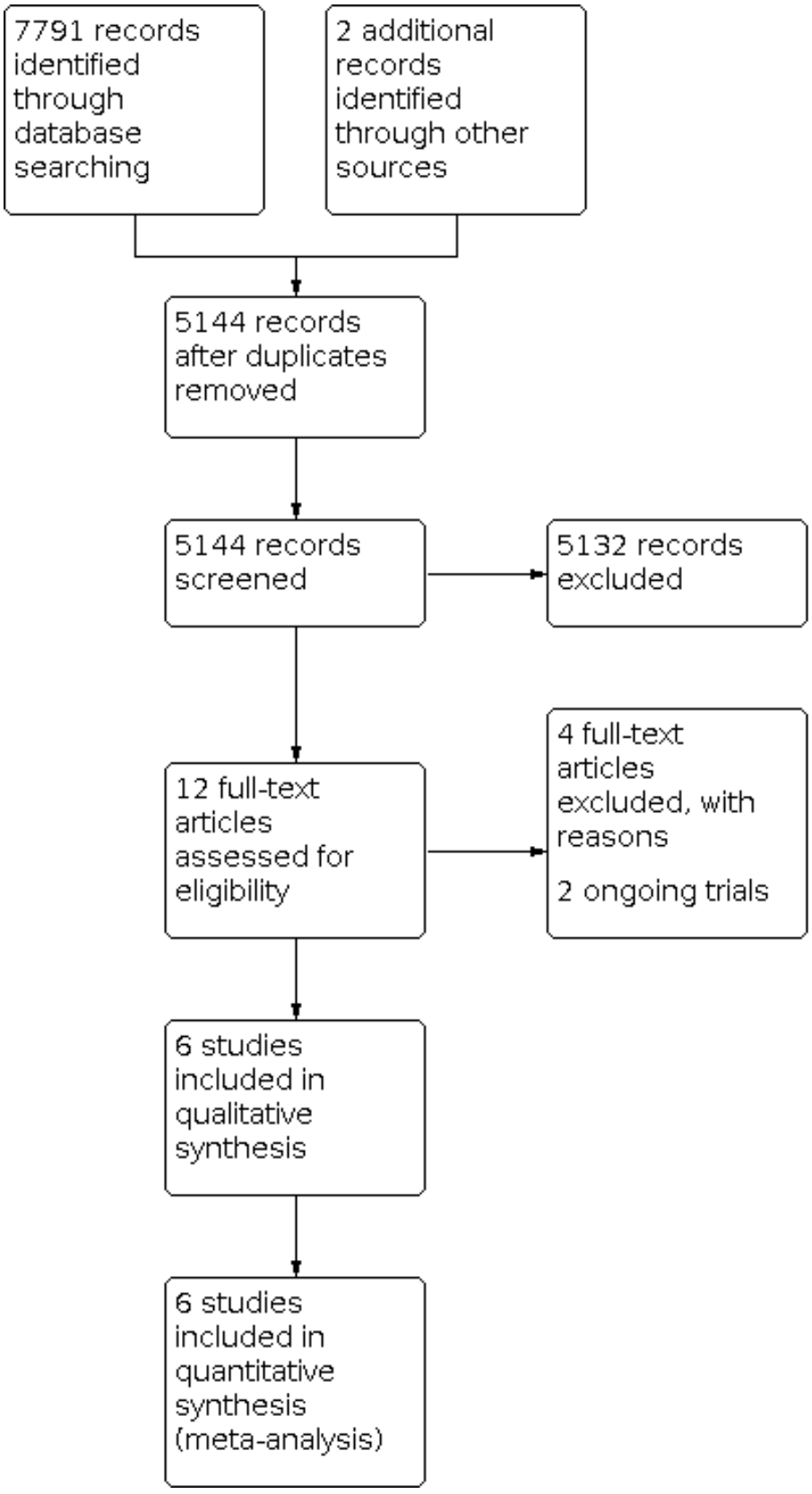
We included six trials (Bora 2017; Chetry 2014; Jajoo 2017; Nangia 2019; Ramya 2014; Sanghvi 2013). Two reports were available as conference abstracts only (Chetry 2014; Jajoo 2017). One was a published dissertation (Ramya 2014).

Results of the search

The search identified 7791 records through database searching and two additional records from other sources. After removing duplicates, 5144 records remained. We excluded 5132 irrelevant

records and assessed the full text of 12 records. We included six RCTs (Bora 2017; Chetry 2014; Jajoo 2017; Nangia 2019; Ramya 2014; Sanghvi 2013; Characteristics of included studies table). We excluded studies with reasons (Genzel-Boroviczény 2002; Higgs 1974; Jain 2016; Yu 1979; Characteristics of excluded studies table), and found two ongoing studies (ISRCTN89654042; NCT03708068; Characteristics of ongoing studies table). See Figure 1.

Figure 1. Study flow diagram.



Included studies

All included trials were undertaken during the 2010s by investigators in neonatal care centres in India (see Characteristics of included studies table).

Participants

In total, 526 infants participated (range per trial 60 to 180). Most were medically stable VLBW infants (birth weight 1000 g to 1500 g) of gestational age at birth 28 to 34 weeks. None was extremely preterm or ELBW. Participants included infants born 'small-for-gestation' in all trials except Chetry 2014, which excluded infants with birth weight less than 3rd percentile for reference population. All trials excluded infants with congenital anomalies or gastrointestinal or neurological problems from participation. Two trials excluded infants in receipt of respiratory support beyond supplemental oxygen (Jajoo 2017; Nangia 2019). One trial excluded infants who needed mechanical ventilation (Sanghvi 2013).

Interventions

The trials compared early full feeding (60 mL/kg to 80 mL/kg on day one after birth) with minimal enteral feeding (typically 20 mL/kg to 30 mL/kg on day one) supplemented with intravenous fluids (typically 10% dextrose). Feed volumes were advanced daily as tolerated by 20 mL/kg to 30 mL/kg body weight to a target steady-state volume of 150 mL/kg/day to 180 mL/kg/day.

All participating infants were fed preferentially with maternal expressed breast milk. Two trials used donor breast milk to supplement insufficient volumes of maternal expressed breast milk (Bora 2017; Ramya 2014). The other trials used preterm formula if maternal milk was insufficient. In three trials, human milk was enriched with a multi-nutrient fortifier when volume of intake exceeded 100 mL/kg/day (Bora 2017; Nangia 2019; Sanghvi 2013).

Outcomes

Outcomes reported most commonly were feed intolerance (reported in various ways but often without accompanying numerical data), days to regain birth weight, duration of birth hospitalisation, necrotising enterocolitis, late-onset infection, and mortality. None of the trials assessed any outcomes posthospitalisation, including growth and neurodevelopment.

Excluded studies

We excluded four studies after full-text assessment (Genzel-Boroviczény 2002; Higgs 1974; Jain 2016; Yu 1979; see Characteristics of excluded studies table).

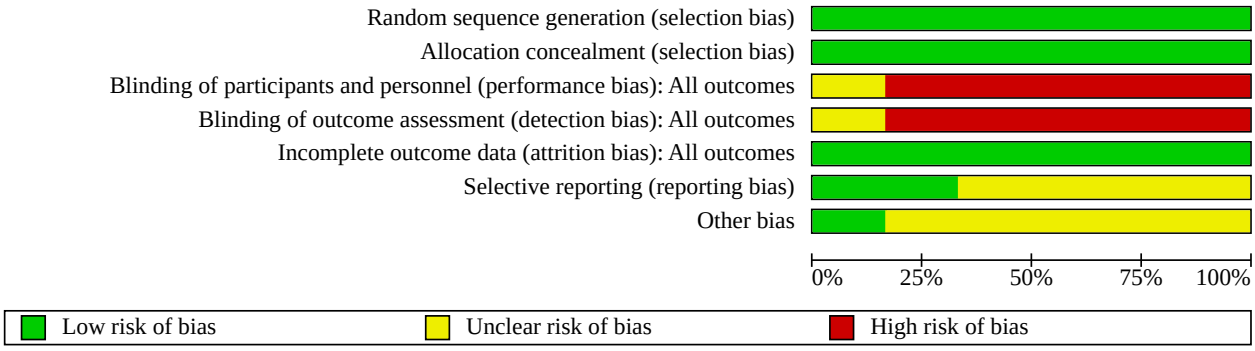
Ongoing studies

We found two ongoing trials (ISRCTN89654042; NCT03708068; see Characteristics of ongoing studies table).

Risk of bias in included studies

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

Figure 2. Risk of bias summary.



Allocation

All trials were at low risk of selection bias as they reported adequate allocation concealment methods (sealed, numbered envelopes).

Blinding

None of the trials masked parents, carers, or clinicians or investigators assessing the trial outcomes (not reported in Sanghvi 2013).

Incomplete outcome data

All trials reported complete outcome assessments of the trial cohorts and were at low risk of attrition bias.

Selective reporting

We were unable to assess reliably whether selective reporting occurred in four of the trials as we identified no trial registrations, protocols, or other indicators of prespecified outcomes; these were at unclear risk of reporting bias (Bora 2017; Chetry 2014; Jajoo 2017; Ramya 2014). The other two trials listed outcomes of interest in their registrations (Nangia 2019; Sanghvi 2013). Both trials reported all prespecified outcomes, and additional, non-prespecified data as secondary outcomes and were at low risk of reporting bias.

Other potential sources of bias

One trial received no funding and was at low risk of other bias (Sanghvi 2013). The others did not report whether they received trial funding and were at unclear risk of other bias.

Effects of interventions

See: **Summary of findings 1** Early full enteral feeding compared to delayed or progressive feeding for preterm or low birth weight infants

Primary outcomes

In hospital rate of weight gain

Two studies reported in hospital rate of weight gain (Chetry 2014 (author correspondence); Nangia 2019).

Chetry 2014 reported a slower rate of weight gain in infants in the early full enteral feeding group (median 15.22 g/kg/day, interquartile range (IQR) 10.9 to 24.6) compared to the incremental feeding group (median 18.23 g/kg/day, IQR 11.36 to 27.3).

Nangia 2019 reported a faster rate of weight gain in the early full enteral feeding group compared with the control group (mean: 6.3 g/kg/day with early full enteral feeding compared to 5.06 g/kg/day with control; SDs not provided).

We did not meta-analyse these data. We assessed the certainty of the evidence as very low, downgrading for risk of bias, inconsistency, and imprecision.

In hospital rate of head circumference growth

None of the trials reported in hospital rate of head circumference growth.

Growth restriction

(Analysis 1.1)

One study reported z-score for weight at hospital discharge (Sanghvi 2013).

The definition of growth restriction in the included trial (z-score at discharge) differed from our prespecified definition (z-score at term). We made a consensus post hoc decision to include the data based on the investigators' definition.

Analysis showed that infants in the early full enteral feeding group had higher z-scores that those in the control group (MD 0.24, 95% CI 0.06 to 0.42).

We assessed the certainty of the evidence as low, downgrading for risk of bias and imprecision.

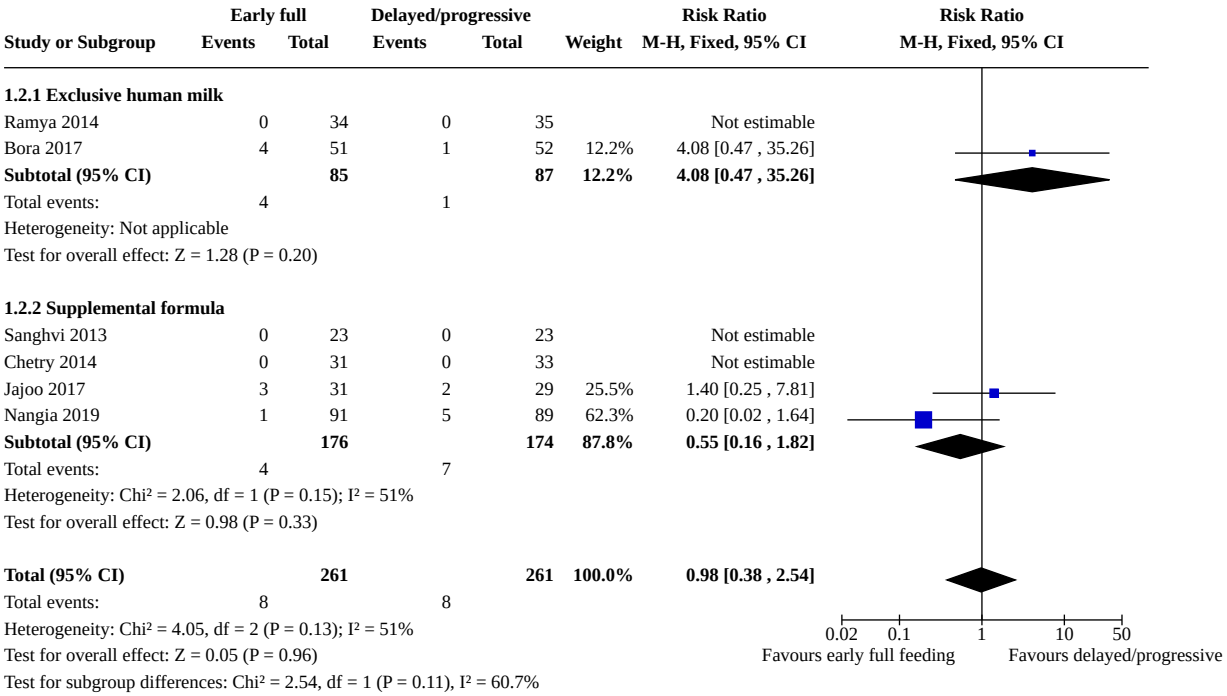
Necrotising enterocolitis

(Analysis 1.2)

Six studies reported necrotising enterocolitis (Bora 2017; Chetry 2014; Jajoo 2017; Nangia 2019; Ramya 2014; Sanghvi 2013). Two trials (which were reported in conference abstracts) did not specify diagnostic criteria for necrotising enterocolitis (Chetry 2014; Jajoo 2017).

There was no evidence of a difference (RR 0.98, 95% CI 0.38 to 2.54; I^2 = 51%; RD −0.00, 95% CI −0.03 to 0.03; Figure 3).

Figure 3. Forest plot of comparison: 1 Early full versus delayed/progressive enteral nutrition, outcome: 1.2 Necrotising enterocolitis.



We assessed the certainty of the evidence as very low, downgrading for risk of bias, inconsistency (moderate heterogeneity), and imprecision.

Secondary outcomes

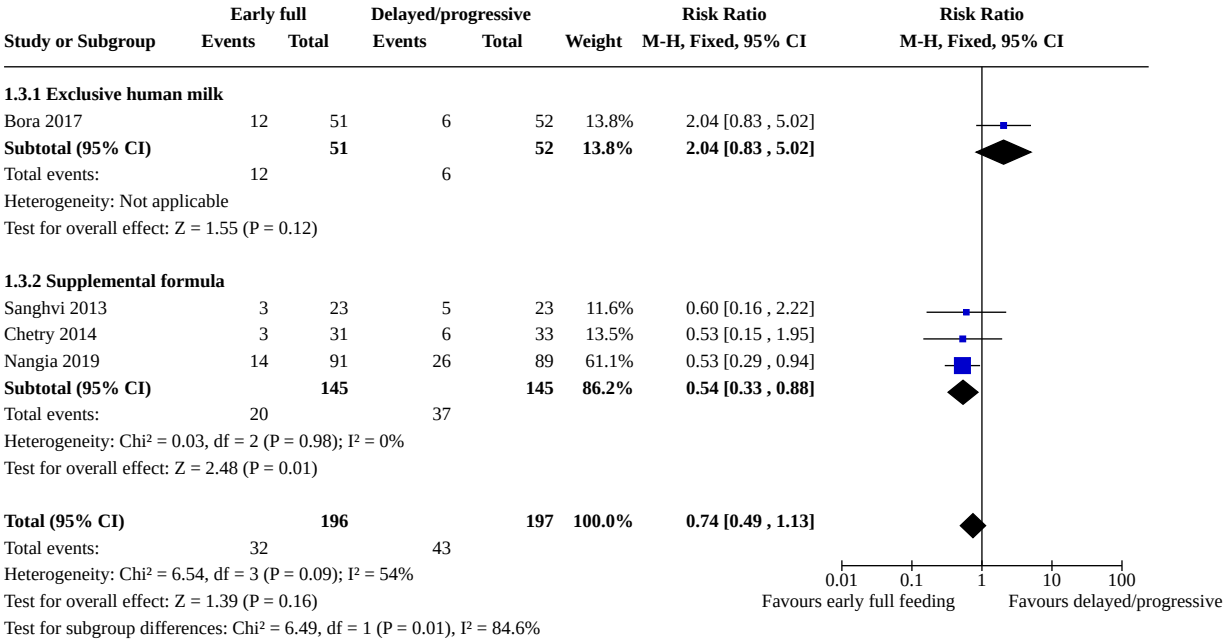
Feed intolerance

(Analysis 1.3)

Four studies reported feed intolerance (Bora 2017; Chetry 2014; Nangia 2019; Sanghvi 2013). The definitions of feed intolerance used in the included trials did not specify the duration of enteral feed interruption. We made a consensus post hoc decision to include the data based on the investigators' definitions (see Characteristics of included studies table).

There was no evidence of a difference (RR 0.74, 95% CI 0.49 to 1.13; I^2 = 54%; RD −0.06, 95% CI −0.13 to 0.02; Figure 4).

Figure 4. Forest plot of comparison: 1 Early full versus delayed/progressive enteral nutrition, outcome: 1.3 Feed intolerance.



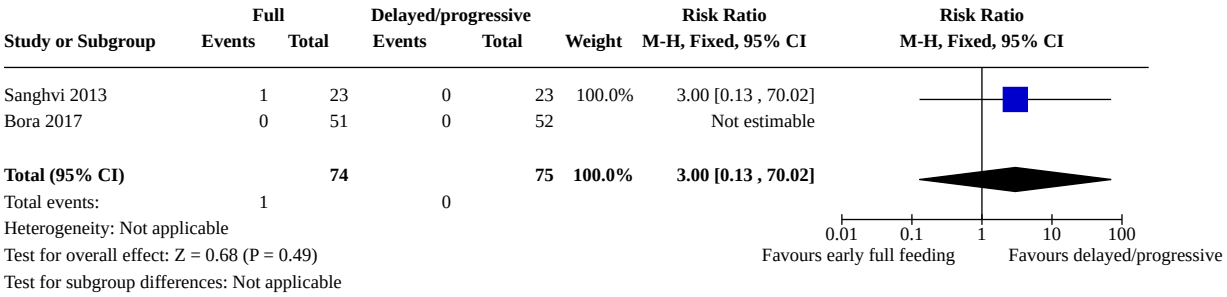
Episodes of hypoglycaemia

(Analysis 1.4)

Two studies reported hypoglycaemia (Nangia 2019; Sanghvi 2013).

There was no evidence of a difference (RR 3.00, 95% CI 0.13 to 70.02; I^2 not estimable; RD 0.01, 95% CI −0.03 to 0.06; Figure 5).

Figure 5. Forest plot of comparison: 1 Early full versus delayed/progressive enteral nutrition, outcome: 1.4 Episodes of hypoglycaemia.



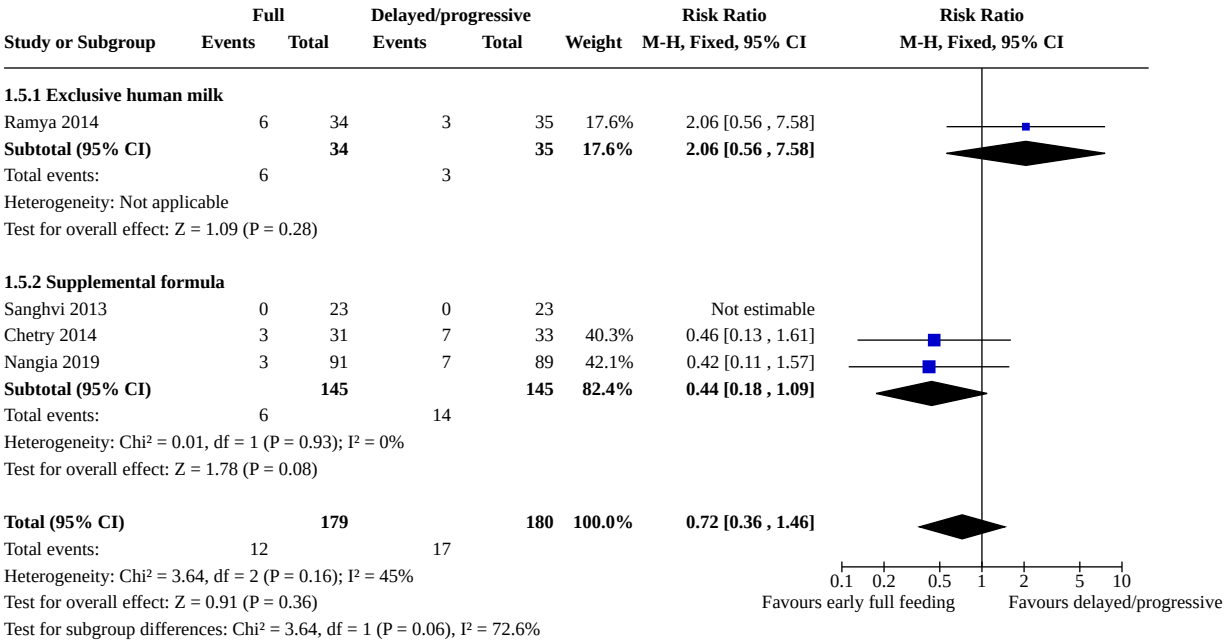
Invasive infection

(Analysis 1.5)

Four studies reported invasive infection (Chetry 2014 (author correspondence); Nangia 2019; Ramya 2014; Sanghvi 2013).

There was no evidence of a difference (RR 0.72, 95% CI 0.36 to 1.46; I^2 = 45%; RD −0.03, 95% CI −0.08 to 0.03; Figure 6).

Figure 6. Forest plot of comparison: 1 Early full versus delayed/progressive enteral nutrition, outcome: 1.5 Invasive infection.



Duration of birth hospitalisation

(Analysis 1.6)

Five studies reported days of hospitalisation (Bora 2017; Chetry 2014; Jajoo 2017; Nangia 2019; Sanghvi 2013).

Meta-analysis showed that the early full enteral feeding group had a shorter duration of hospitalisation than infants in the control group (MD −3.07 days, 95% CI −4.13 to −2.02; I^2 = 90%).

All-cause mortality

(Analysis 1.7)

Six studies reported mortality (Bora 2017 (author correspondence); Chetry 2014 (author correspondence); Jajoo 2017; Nangia 2019; Ramya 2014; Sanghvi 2013).

There was no evidence of a difference (RR 0.78, 95% CI 0.36 to 1.70; I^2 = 0%; RD −0.01, 95% CI −0.05 to 0.03).

Long-term growth

None of the studies reported long-term growth.

Severe neurodevelopmental disability

None of the studies reported severe neurodevelopmental disability.

Additional post hoc outcome

Days to regain birth weight

(Analysis 1.8)

Six studies reported days to regain birth weight (Bora 2017; Chetry 2014; Jajoo 2017; Nangia 2019; Ramya 2014; Sanghvi 2013).

Meta-analysis showed that the early full enteral feeds group regained birth weight earlier than the control group (MD −3.42 days, 95% CI −4.31 to −2.53; I^2 = 89%).

Subgroup analyses

1. Trials in which infants received human milk only versus those where formula could be given instead of, or as a supplement to, human milk. The test for subgroup differences was statistically significant for:
   a. feed intolerance (Chi^2 = 6.49, df = 1 (P = 0.01), I^2 = 84.6%); Figure 4):
      i. exclusive human milk: RR 2.04, 95% CI 0.83 to 5.02; I^2 = not applicable; RD −0.12, 95% CI −0.03 to 0.27;
      ii. supplemental formula: RR 0.54, 95% CI 0.33 to 0.88; I^2 = 0%; RD −0.12, 95% CI −0.21 to -0.03
   b. duration of hospitalisation (Chi^2 = 22.73, df = 1 (P < 0.00001), I^2 = 95.6%;):
      i. exclusive human milk: MD −1.40 days, 95% CI −2.66 to −1.04 days; I^2 = not applicable;
      ii. supplemental formula: MD −7.03 days, 95% CI −8.96 to −5.09 days; I^2 = 82%;
   c. days to regain birth weight (Chi^2 = 4.25, df = 1 (P = 0.04), I^2 = 76.5%):
      i. exclusive human milk: MD −1.97, 95% CI −3.67 to −0.26 days; I^2 = 0%;
      ii. Supplemental formula: MD −4.02, 95% CI −4.98 to −3.07 days; I^2 = 91%.
2. Very preterm infants (born at less than 32 weeks' gestation) versus infants born at 32 weeks' gestation or greater.
   a. Subgroup data not available (most trial participants were very preterm infant).

3. Very low birth weight infants (less than 1500 g) versus infants with a birth weight of 1500 g or greater.
   a. All trial participants were very low birth weight infants (1000 g to 1500 g).
4. Infants with a birth weight below the 10th percentile for the reference population ('small for gestation') versus infants with a birth weight at or above the 10th percentile ('appropriate for gestation').
   a. Subgroup data for infants born 'small for gestation' not available.
5. Trials set in low- or middle-income countries versus trials set in high-income countries.
   a. All the trials were conducted in a middle-income country (India).

Sensitivity analysis for risk of bias

We were unable to do planned sensitivity analyses to determine if the findings were affected by bias as the trials had a similar risk of bias with low risk for randomisation and allocation concealment, complete or near-complete follow-up, but high risk from inadequate masking of intervention and measurement.

DISCUSSION

Summary of main results

Data from six trials, in which 526 VLBW infants participated, provided limited evidence about the effect of early full enteral feeding on growth and development. There are data from two trials on in hospital rates of weight gain, and these have inconsistent results (not suitable to be combined in meta-analysis). One trial that assessed infant weight at the time of hospital discharge showed that early enteral feeding slightly increased the mean z-score compared with delayed or progressive advancement of enteral feeds. There are no data on head growth or length at hospital discharge, or for growth parameters following discharge and developmental outcomes assessed beyond infancy.

The growth parameter most commonly reported was the time from birth to regain birth weight. We did not prespecify this outcome, but a post hoc meta-analysis of data from six trials showed that infants who had early full enteral feeding regained birth weight about three days earlier than infants who had delayed introduction and progressive advancement of feed volumes. Given the paucity of data for other growth parameters, however, the importance of this effect is unclear.

Meta-analysis of data from six trials found no effect of early full enteral feeding on risk of necrotising enterocolitis. The bounds of the 95% CI for the RD are consistent with either three extra or three fewer cases in every 100 infants who receive early full enteral feeding. We found no evidence of other possible benefits or harms, including insufficient data to determine whether early full enteral feeding is associated with the risk of feed intolerance, invasive infection, duration of birth hospitalisation, mortality, or episodes of hypoglycaemia during the early neonatal period.

Overall completeness and applicability of evidence

Most participants included in the six trials in this review were stable very preterm infants of birth weight between 1000 g and 1500 g. One trial excluded infants who were born 'small for gestation' from participation (Chetry 2014). Two trials excluded infants with evidence of intrauterine growth compromise indicated by the antenatal detection of absent or reversed end-diastolic flow velocity in the umbilical vessels (Nangia 2019; Ramya 2014). The other trials did not report subgroup data for infants who were 'small for gestation' or growth restricted at birth. It is unclear, therefore, whether the review findings are applicable to infants who have both a high level of nutrient requirement and an elevated risk of developing necrotising enterocolitis (Dorling 2005; Samuels 2017).

In two trials, infants received only human milk (expressed own mother's milk or donor milk) (Bora 2017; Ramya 2014). The other trials used maternal milk preferentially, but used cow's milk formula to supplement any deficits (Chetry 2014; Jajoo 2017; Nangia 2019; Sanghvi 2013). The risk-benefit balance of early enteral feeding strategies may differ between human milk-fed and formula-fed very preterm or VLBW infants (Quigley 2019). Prespecified subgroup analyses, however, found no differences on the risk of necrotising enterocolitis or death between infants who received human milk only versus those where formula could be given instead of, or as a supplement to, human milk.

All the trials included in this review were conducted in neonatal care facilities in India in the 2010s. The review findings may be applicable particularly to neonatal care facilities where staff and equipment costs limit the availability of parenteral fluids or nutrition, as well as to facilities without such resource constraints where early full enteral feeding could complement other infant and family centred care practices (Patel 2018).

Quality of the evidence

The certainty of evidence for the primary outcomes, assessed using GRADE methods, was low or very low, downgraded because of risk of bias in the included trials (lack of masking of investigators, parents, and carers), imprecision of estimates of effect, and inconsistency (heterogeneity) in meta-analyses (Summary of findings 1).

Risk of bias (lack of masking)

In all the included trials, staff and parents knew to which group the participating infant had been allocated (because it is difficult to conceal intravenous access devices and fluids). Lack of masking may have resulted in surveillance and detection biases. It is unclear, however, to what extent lack of masking might have biased effect estimates. It is plausible that clinicians who harboured concerns that early full enteral feeding could contribute to feed intolerance or necrotising enterocolitis, for example, might have undertaken more assessments or tests, or used a lower threshold for subjective criteria, to diagnose these conditions.

Inconsistency (heterogeneity) in meta-analyses

The meta-analyses in this review showed moderate to high levels of statistical heterogeneity that were not explained by major differences in trial design or conduct. All the trials were undertaken in secondary care facilities in India during the 2010s. Participants were similar (stable very preterm infants of birth weight between 1000 g and 1500 g). Trials used slightly different rates of advancement of feed volumes, but these were consistent with current practice (20 mL/kg to 30 mL/kg). Trials differed by the modality of intravenous fluids in the control group, with two trials providing parenteral nutrition and four providing 10%

dextrose. Given the duration of use of intravenous fluid (up to one week), this may have affected growth outcomes.

The assessed outcomes were similar across the trials. For some outcomes, such as feed intolerance and necrotising enterocolitis, diagnosed using subjective criteria, variation in diagnostic thresholds might be a source of heterogeneity. As these criteria were not explicitly described in all the published reports, we were unable to explore the extent to which variation in outcome definition contributed to inconsistency in estimates of effect.

In prespecified subgroup comparisons of trials in which infants received human milk only versus those where formula could be given as a supplement to human milk, there was no evidence of a differential effect on the risk of necrotising enterocolitis. Small subgroup differences exist for the risk of feed intolerance and time taken to regain birth weight. The subgroup difference in the estimates of effect on the duration of hospitalisation favoured trials in which formula was used as a supplement when maternal milk was insufficient. This might be due to accelerated weight gain in infants receiving preterm formula with higher nutrient density than human milk. Since an attained body weight (ranging from 1300 g to 1600 g across trials) was a key discharge criterion for participants, infants reaching those targets earlier will have shorted durations of hospitalisation.

Imprecision

The estimates of effect were imprecise as indicated by the broad 95% CIs with upper and lower bounds encompassing substantial harm or benefit. This reflects the sample size of the studied population (526 infants in total), the rarity of the key outcomes such as necrotising enterocolitis (3% overall rate in the control groups), and the paucity of outcome data, especially of growth parameters, available for synthesis due to non-reporting. Ongoing trials of this intervention should recruit sufficient participants to provide data to optimise the information size in future meta-analyses.

Potential biases in the review process

The main concern is the possibility that findings of this review 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 (yet) published in full form in academic journals. There were insufficient trials to examine for symmetry of funnel plots as a means of identifying possible publication or small-study bias.

Agreements and disagreements with other studies or reviews

This review focused on the comparison of early full enteral feeding versus delayed introduction or progressive feed volume advancement. Other Cochrane Reviews have appraised and synthesised the trial evidence for the comparison of different rates of volume advancement and different timing of introduction of progressive enteral feeds. Consistent with the findings of this review, these show that conservative feeding strategies (delaying introduction of enteral feeds until beyond four days after birth, or advancing feed volumes more slowly than by 24 mL/kg daily) do not affect growth parameters or the risk of feed intolerance or necrotising enterocolitis in very preterm infants (Morgan 2014; Oddie 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The available trial data do not provide sufficient data to determine how early full enteral feeding, compared with delayed or gradual introduction of enteral feeds (combined with parenteral fluids or nutrition) affects growth and development in preterm or low birth weight infants. While meta-analyses found no effects on the risk of necrotising enterocolitis, feed intolerance, late onset infection, or death in preterm or low birth weight infants, the certainty of the evidence is low or very low.

Implications for research

Given the potential for early full enteral feeding to affect important outcomes in preterm or low birth weight infants, this intervention merits further assessment in pragmatic randomised trials powered to detect important effects on growth, as well as potential adverse consequences such as necrotising enterocolitis. One such trial is being conducted in the UK (FEED1) (ISRCTN89654042).

ACKNOWLEDGEMENTS

We would like to thank Cochrane Neonatal: Colleen Ovelman, Managing Editor; Jane Cracknell, Assistant Managing Editor; and Roger Soll, Co-coordinating editor, who provided editorial and administrative support.

David Osborn (Cochrane Neonatal Editor) and Thangaraj Abiramalatha (peer reviewer) provided feedback.

We thank Drs Satish Saluja, Mamta Jajoo, and Sushma Nangia for providing unpublished information about their trials (Chetry 2014; Jajoo 2017; Nangia 2019).

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CHARACTERISTICS OF STUDIES

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

Bora 2017

Study characteristics	
Methods	Randomised controlled trial
Participants	107 "stable" VLBW infants (1000–1500 g birth weight), irrespective of gestational age at birth Setting: Department of Paediatrics, Assam Medical College, Assam, India
Interventions	Intervention (n = 52): full enteral feeds (80 mL/kg/day) with expressed breast milk or donor breast milk Control (n = 55): minimal enteral feeds (20 mL/kg/day) supplemented with intravenous 10% dextrose

Bora 2017 *(Continued)*

	Feed volumes increased by 20 mL/kg/day as tolerated
Outcomes	1. Feed intolerance (vomiting > 3 times/24 hours, or bile or blood-stained vomit, or abdominal girth increase > 2 cm, or prefeed gastric aspirate > 50% previous feed volume, or altered aspirate, or abdominal wall erythema, or gross blood in stools) 2. Necrotising enterocolitis (Bell's criteria) 3. Days to regain birth weight
Notes	Human milk was enriched with a multi-nutrient fortifier when infants reached an intake volume of volume of 100 mL/kg/day. The intervention group contained more infants born to mothers with pregnancy induced hypertension (51%) than the control group (31%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not masked.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete (103/107 participants).
Selective reporting (reporting bias)	Unclear risk	No protocol to compare. All outcomes in methods section reported.
Other bias	Unclear risk	No funding source reported.

Chetry 2014

Study characteristics

Methods	Randomised controlled trial
Participants	64 "stable" VLBW infants (1000–1500 g birth weight), of gestational age 30–34 weeks at birth, and > 3rd percentile for weight Setting: Sir Ganga Ram Hospital, New Delhi, India
Interventions	Intervention (n = 31): full enteral feeds (80 mL/kg/day) with expressed breast milk if available or preterm formula Control (n = 33): minimal enteral feeds (20 mL/kg/day) supplemented with parenteral nutrition

Chetry 2014 *(Continued)*

	Feed volumes increased by 20 mL/kg/day subject as tolerated
Outcomes	1. Feed intolerance (not defined) 2. Necrotising enterocolitis (Bell's criteria) 3. Days to regain birth weight 4. Invasive infection (blood culture) 5. Duration of hospitalisation
Notes	Further information via author communication (satishsaluja@gmail.com)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not masked.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete.
Selective reporting (reporting bias)	Unclear risk	Abstract and author correspondence only. No protocol or methods to compare outcomes reported.
Other bias	Unclear risk	No definition given for necrotising enterocolitis. Funding source not reported.

Jajoo 2017

Study characteristics

Methods	Randomised controlled trial
Participants	60 "stable" VLBW (1000–1499 g birth weight), of gestational age 29–33 weeks at birth Setting: Department of Paediatrics, Chacha Nehru Bal Chikitsalaya, New Delhi, India
Interventions	Intervention (n = 31): full enteral feeds (80 mL/kg/day) with expressed maternal milk or formula Control (n = 29): minimal enteral feeds (30 mL/kg/day) supplemented with intravenous 10% dextrose Feed volumes increased by 20 mL/kg/day as tolerated

Jajoo 2017 *(Continued)*

Outcomes	1. Days to achieve full feeds (180 mL/kg/day) 2. Days to regain birth weight (SD imputed from Chetry 2014) 3. Necrotising enterocolitis (Bell's criteria) 4. Duration of hospitalisation (SD imputed from Chetry 2014)
Notes	Further information via author communication (mamtajajoo123@gmail.com)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unlikely to have been masked.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unlikely to have been masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete.
Selective reporting (reporting bias)	Unclear risk	Abstract only. No protocol available to compare. Additional to primary and secondary outcome in methods section, they reported duration of hospital stay and mortality.
Other bias	Unclear risk	Funding source not reported.

Nangia 2019

Study characteristics

Methods	Randomised controlled trial
Participants	180 "stable" VLBW infants (1000–1499 g birth weight), of gestational age 28–34 weeks at birth Setting: Department of Neonatology, Lady Hardinge Medical College, New Delhi, India
Interventions	Intervention (n = 91): full enteral feeds (80 mL/kg/day) with expressed breast milk or preterm formula Control (n = 89): minimal enteral feeds (20 mL/kg/day) supplemented with intravenous 10% dextrose Feed volumes advanced by 20 mL/kg/day for 2 days, then 30 mL/kg/day
Outcomes	1. Days to achieve full feeds (150 mL/kg/day) 2. Feed intolerance 3. Necrotising enterocolitis

Nangia 2019 *(Continued)*

	4. Days to regain birth weight 5. Invasive infection 6. Duration of hospital stay
Notes	Human milk was enriched with a multi-nutrient fortifier when infants reached an intake volume of volume of 100 mL/kg/day.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not masked.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete.
Selective reporting (reporting bias)	Low risk	All outcomes on trial registry reported. Additional data not specified as outcomes in trial registry also reported as secondary outcomes (necrotising enterocolitis, days to regain birth weight, discharge weight, hyperglycaemia, hypoglycaemia, patent ductus arteriosus, apnoea, duration of antibiotics, duration of intravenous fluids, intraventricular haemorrhage, shock).
Other bias	Unclear risk	Funding source not reported.

Ramya 2014

Study characteristics

Methods	Randomised controlled trial
Participants	69 stable VLBW infants (1000–1500 g birth weight) Setting: Madras Medical College, Chennai, Tamil Nadu, India
Interventions	Intervention (n = 34): full enteral feeds (60 mL/kg/day) with expressed maternal milk or donor breast milk Control (n = 35): minimal enteral feeds (20–40 mL/kg/day) supplemented with parenteral nutrition Feed volumes advanced by 20 mL/kg/day as tolerated
Outcomes	1. Days to regain birth weight

Ramya 2014 *(Continued)*

	2. Feed intolerance (feeds ceased for prefeed gastric aspirates > 50% of prior feed volume, increase in abdominal girth > 2 cm, visible dilated bowel loops or significant emesis, blood tinged or coffee ground aspirate) 3. Necrotising enterocolitis (Bell's criteria) 4. Invasive infection 5. Duration of hospital stay
Notes	Nutrient fortifiers not used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not masked.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete.
Selective reporting (reporting bias)	Unclear risk	No protocol.
Other bias	Unclear risk	Study for dissertation submitted to University for DM (Neonatology). No funding source reported.

Sanghvi 2013

Study characteristics

Methods	Randomised controlled trial
Participants	46 VLBW infants (1200–1500 g birth weight), irrespective of gestational age at birth Setting: Prince Aly Khan Hospital, Mumbai, India
Interventions	Intervention (n = 23): full enteral feeds (80 mL/kg/day) with expressed maternal milk or preterm formula Control (n = 23): minimal enteral feeds (20 mL/kg/day) supplemented with parenteral nutrition Feed volumes increased by 20 mL/kg/day as tolerated
Outcomes	1. Days to regain birth weight

Sanghvi 2013 *(Continued)*

	2. Feed intolerance (feed volume reduce if 6-hourly gastric aspirate > 30% of prior feed volume, increase in abdominal girth, vomiting) 3. Necrotising enterocolitis (not defined – no cases in either group) 4. Invasive infection 5. Duration of hospital stay
Notes	Human milk was enriched with a multi-nutrient fortifier when infants reached an intake volume of volume of 100 mL/kg/day. Fewer infants in the intervention group than the control group received respiratory support via a continuous positive airway pressure device.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated (variable block size randomisation, generated by statistician who was not part of the study).
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not masked – carers could not be blinded to treatment allocation because of nature of the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete.
Selective reporting (reporting bias)	Low risk	Retrospectively registered (2012). All outcomes reported in trial registry reported. Reported additional outcomes of feeding intolerance, weight at discharge, z-score of weight at discharge, length and head circumference at discharge.
Other bias	Low risk	Received no monetary support.

n: number of participants; SD: standard deviation; VLBW: very low birth weight.

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

Study	Reason for exclusion
Genzel-Boroviczény 2002	Non-randomised observational study comparing apolipoprotein A1 and high-density lipoprotein distributions in 3 groups of infants (infants with parenteral nutrition receiving early feedings, preterm infants and term infants receiving enteral nutrition).
Higgs 1974	Did not meet inclusion criteria for intervention and comparator. Intervention of total parenteral nutrition was compared to a milk feeding regimen supplemented with intravenous dextrose.

Study	Reason for exclusion
Jain 2016	Did not meet inclusion criteria for intervention and comparator. This study compared the speed of increasing milk feeds supplemented by intravenous dextrose/parenteral nutrition.
Yu 1979	Did not meet inclusion criteria for intervention and comparator. Intervention of total parenteral nutrition was compared to a milk feeding regimen supplemented with intravenous dextrose.

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

ISRCTN89654042

Study name	Fluids exclusively enterally from day one in premature infants
Methods	Randomised controlled trial
Participants	Preterm infants born at 30–32 completed weeks' gestation
Interventions	Intervention: full milk feeds (minimum of 60 mL/kg each day) from day 1 Control: maximum of 30 mL/kg from day 1 along with intravenous fluids/nutrition as per usual care
Outcomes	Primary outcome: duration of birth hospitalisation
Starting date	2019
Contact information	Garry Meakin, University of Nottingham, UK
Notes	Sample size: 2080

NCT03708068

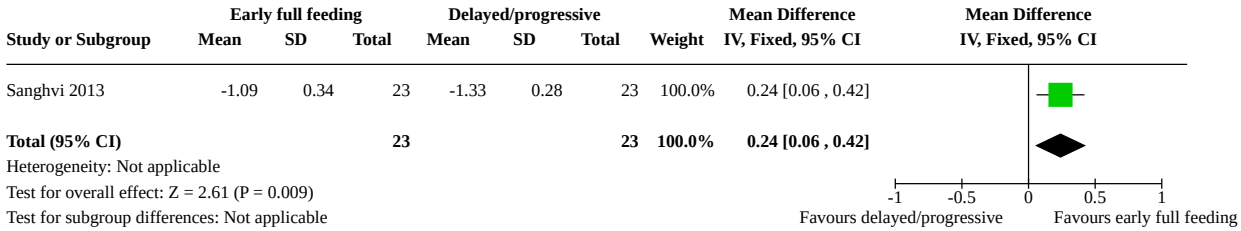
Study name	Early exclusive enteral nutrition in early preterm infants
Methods	Randomised controlled trial
Participants	Preterm infants born at 30–33 completed weeks' gestation, and of birth weight > 1000 g
Interventions	Intervention: early full enteral feeds: feeds commence at ≥ 80% of reference daily fluid intake from day 1 Control: enteral feeds commence at 15–30 mL/kg on day 1, then advanced by 15–30 mL/kg per day on second day onwards until infant reaches full enteral feeds
Outcomes	Primary outcome: time to achieve full enteral feeds defined as 140 mL/kg/day sustained for ≥ 3 days
Starting date	2019
Contact information	Belal Alshaikh, University of Calgary, Canada
Notes	Sample size: 68

DATA AND ANALYSES

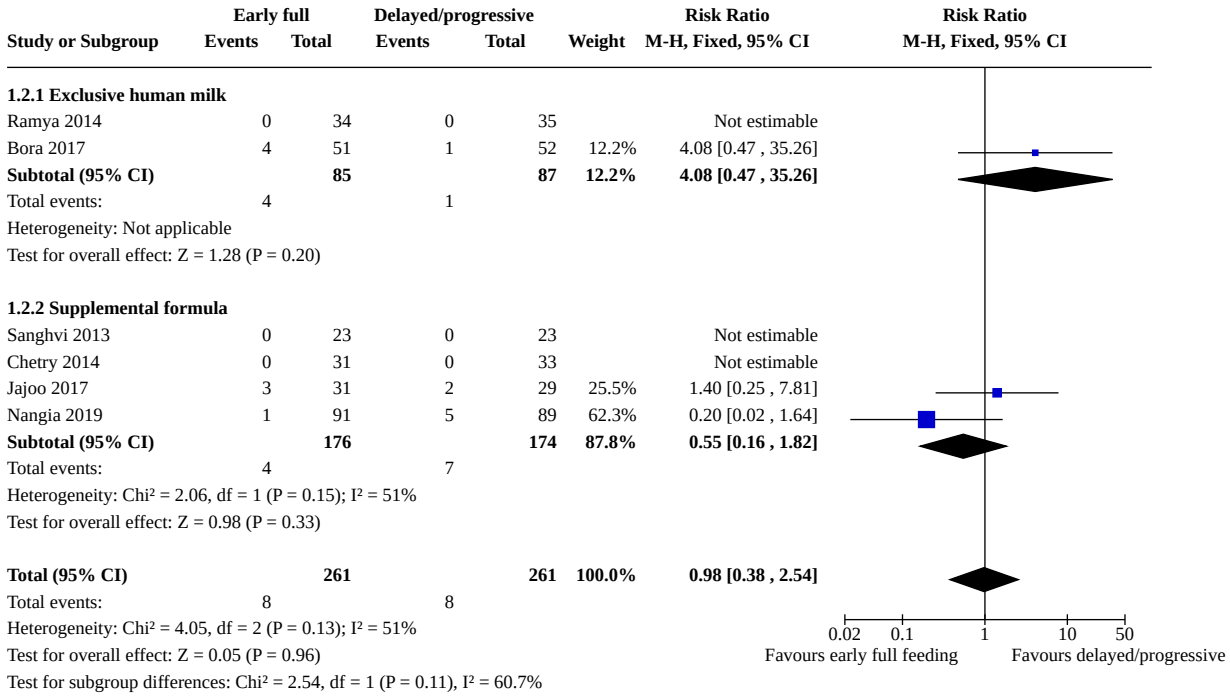
Comparison 1. Early full versus delayed/progressive enteral nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 z-score for weight at hospital discharge	1	46	Mean Difference (IV, Fixed, 95% CI)	0.24 [0.06, 0.42]
1.2 Necrotising enterocolitis	6	522	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.38, 2.54]
1.2.1 Exclusive human milk	2	172	Risk Ratio (M-H, Fixed, 95% CI)	4.08 [0.47, 35.26]
1.2.2 Supplemental formula	4	350	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.16, 1.82]
1.3 Feed intolerance	4	393	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.49, 1.13]
1.3.1 Exclusive human milk	1	103	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.83, 5.02]
1.3.2 Supplemental formula	3	290	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.33, 0.88]
1.4 Episodes of hypoglycaemia	2	149	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.02]
1.5 Invasive infection	4	359	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.36, 1.46]
1.5.1 Exclusive human milk	1	69	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.56, 7.58]
1.5.2 Supplemental formula	3	290	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.18, 1.09]
1.6 Duration of birth hospitalisation (days)	5	436	Mean Difference (IV, Fixed, 95% CI)	-3.07 [-4.13, -2.02]
1.6.1 Exclusive human milk	1	103	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.66, -0.14]
1.6.2 Supplemental formula	4	333	Mean Difference (IV, Fixed, 95% CI)	-7.03 [-8.96, -5.09]
1.7 All-cause mortality	6	522	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.70]
1.7.1 Exclusive human milk	2	172	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.29, 3.59]
1.7.2 Supplemental formula	4	350	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.24, 1.80]
1.8 Days to regain birth weight	6	505	Mean Difference (IV, Fixed, 95% CI)	-3.53 [-4.37, -2.70]
1.8.1 Exclusive human milk	2	168	Mean Difference (IV, Fixed, 95% CI)	-1.97 [-3.67, -0.26]
1.8.2 Supplemental formula	4	337	Mean Difference (IV, Fixed, 95% CI)	-4.02 [-4.98, -3.07]

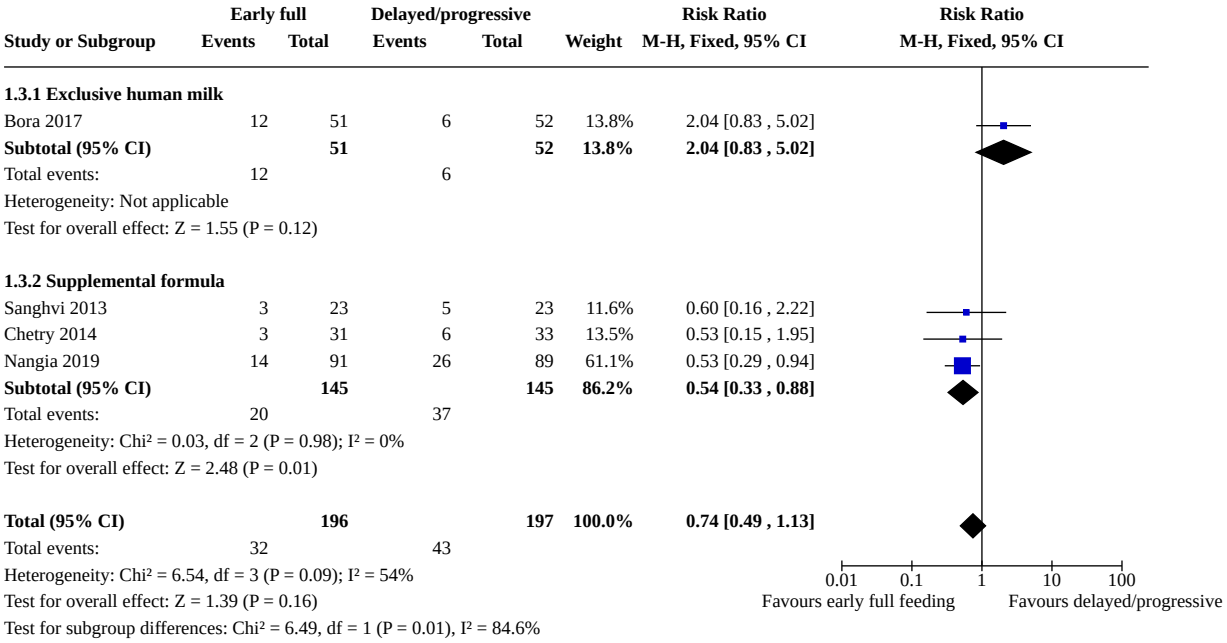
Analysis 1.1. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 1: z-score for weight at hospital discharge



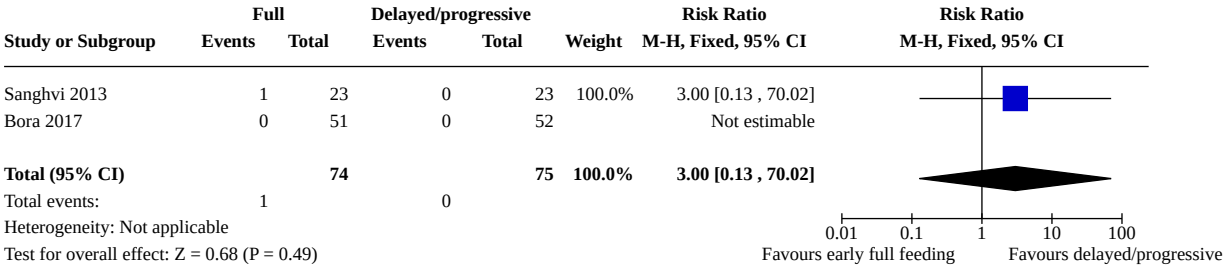
Analysis 1.2. Comparison 1: Early full versus delayed/ progressive enteral nutrition, Outcome 2: Necrotising enterocolitis



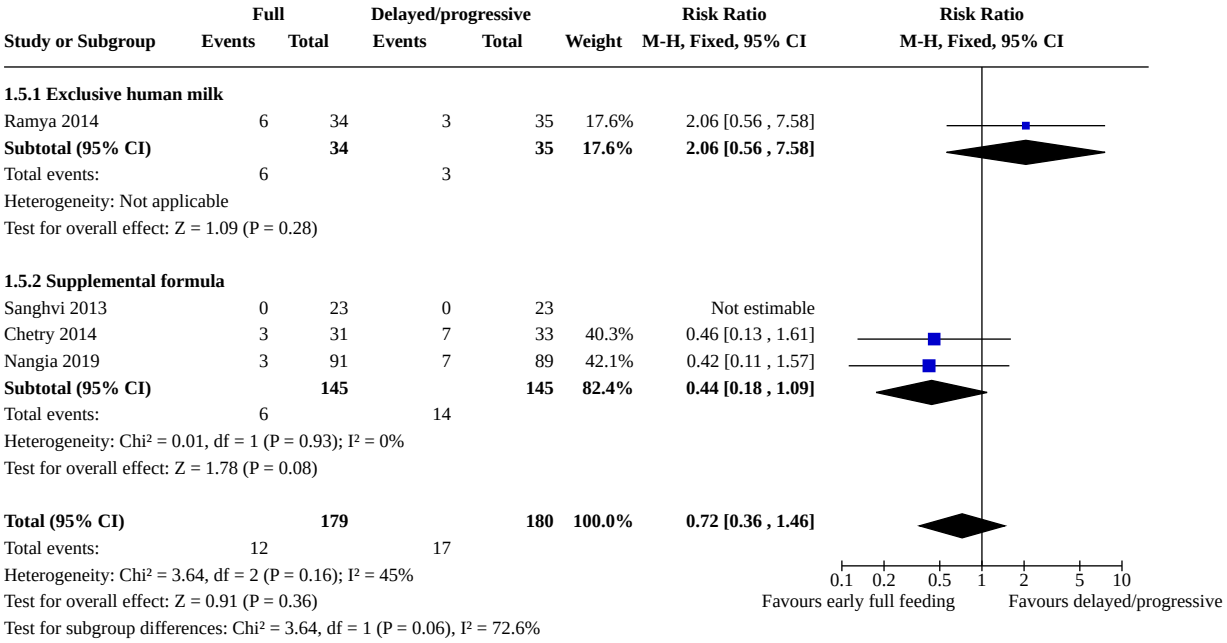
Analysis 1.3. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 3: Feed intolerance



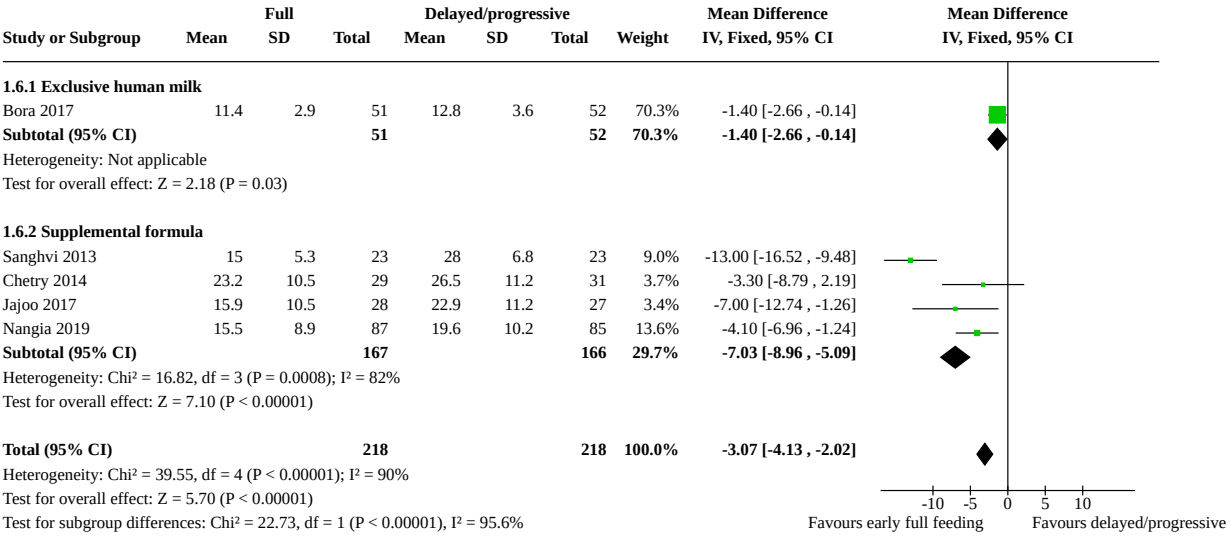
Analysis 1.4. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 4: Episodes of hypoglycaemia



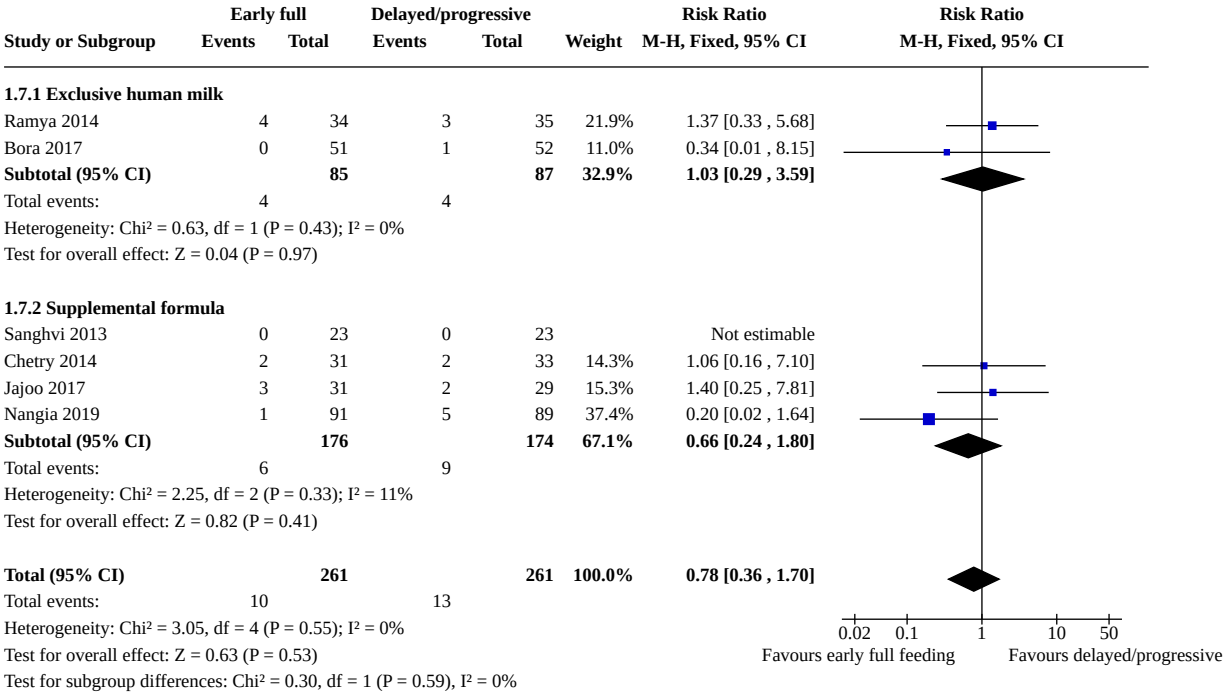
Analysis 1.5. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 5: Invasive infection



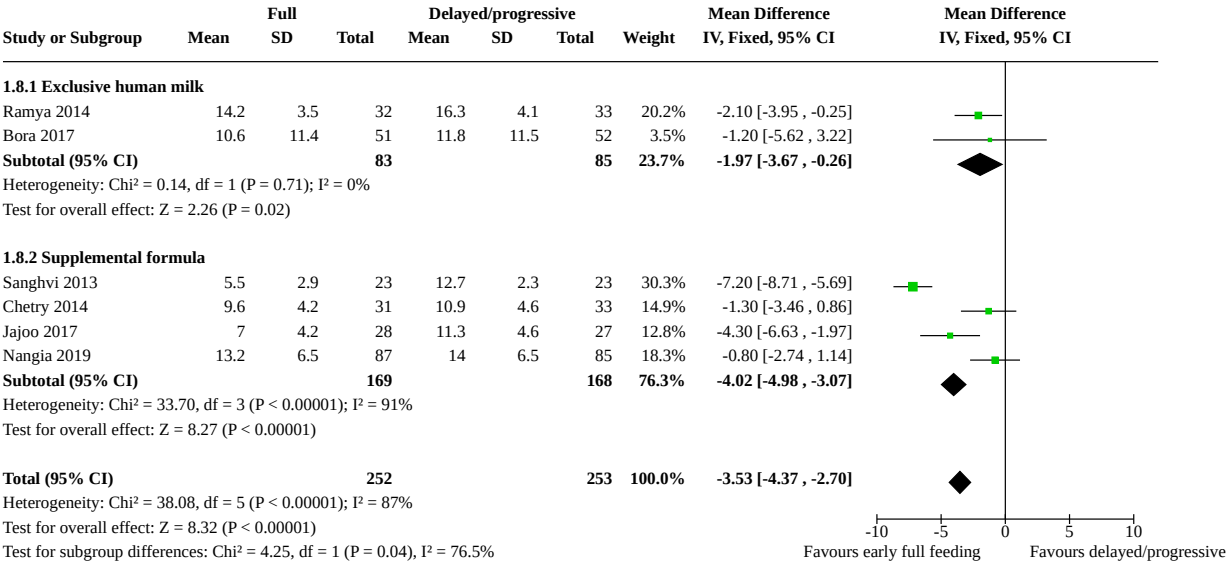
Analysis 1.6. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 6: Duration of birth hospitalisation (days)



Analysis 1.7. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 7: All-cause mortality



Analysis 1.8. Comparison 1: Early full versus delayed/progressive enteral nutrition, Outcome 8: Days to regain birth weight



APPENDICES

Appendix 1. Electronic search strategy

CENTRAL via the Cochrane Library

Search date 19 October 2020

ID Search

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

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

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

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

#5 #1 OR #2 OR #3 OR #4

#6 MeSH descriptor: [Enteral Nutrition] explode all trees

#7 (((enteral or enteric) NEAR/2 (nutrition or feed*))):ti,ab,kw OR (((oral or sip or tube) NEAR/2 feeding*)):ti,ab,kw OR (((nasogastric or gastrostomy or jejunostomy) NEAR/2 tube*)):ti,ab,kw OR (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) NEAR/3 enteral feed*)):ti,ab,kw OR (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) NEAR/3 enteric feed*)):ti,ab,kw (Word variations have been searched)

#8 (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) NEAR/3 enteral intake*)):ti,ab,kw OR (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) NEAR/3 enteric intake*)):ti,ab,kw OR (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) NEAR/3 enteral nutrition)):ti,ab,kw OR (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) NEAR/3 enteric nutrition)):ti,ab,kw OR (((aggressive* or fast or rapid* or slow* or speed*) NEAR/3 feed*)):ti,ab,kw (Word variations have been searched)

#9 (((aggressive* or fast or rapid* or slow* or speed*) NEAR/3 volume*)):ti,ab,kw OR (trophic feeding*):ti,ab,kw OR (((gut or gastrointestinal) NEAR/2 priming)):ti,ab,kw (Word variations have been searched)

#10 #6 or #7 or #8 or #9

#11 #5 and #10

#12 MeSH descriptor: [Parenteral Nutrition] explode all trees and with qualifier(s): [adverse effects - AE]

#13 MeSH descriptor: [Enterocolitis, Necrotizing] explode all trees and with qualifier(s): [etiology - ET, epidemiology - EP, prevention & control - PC]

#14 MeSH descriptor: [Infections] 1 tree(s) exploded and with qualifier(s): [epidemiology - EP]

#15 (((prevent* or risk*) NEAR/3 necrotising enterocolitis)):ti,ab,kw OR (((prevent* or risk*) NEAR/3 necrotizing enterocolitis)):ti,ab,kw (Word variations have been searched)

#16 #12 or #13 or #14 or #15

#17 #5 and #16

#18 #11 or #17

CINAHL via EBSCO

Search date 19 October 2020

S1 (MH "Infant, Newborn+")

S2 (MH "Childbirth, Premature")

S3 TI ((neonat* or neo nat*)) OR AB ((neonat* or neo nat*)) OR TI ((newborn* or new born* or newly born*)) OR AB ((newborn* or new born* or newly born*)) OR TI ((preterm or preterms or pre term or pre terms)) OR AB ((preterm or preterms or pre term or pre terms))

S4 TI ((preemie* or premie or premies)) OR AB ((preemie* or premie or premies)) OR TI ((prematur* N3 (birth* or born or deliver*))) OR AB ((prematur* N3 (birth* or born or deliver*))) OR TI ((low N3 (birthweight* or birth weight*))) OR AB ((low N3 (birthweight* or birth weight*)))

S5 TI ((lbw or vlbw or elbw)) OR AB ((lbw or vlbw or elbw)) OR TI infan* OR AB infan* OR TI ((baby or babies)) OR AB ((baby or babies))

S6 S1 OR S2 OR S3 OR S4 OR S5

S7 (MH "Enteral Nutrition")

S8 TI (((enteral or enteric) N2 (nutrition or feed*))) OR AB (((enteral or enteric) N2 (nutrition or feed*))) OR TI (((oral or sip or tube) N2 feeding*)) OR AB (((oral or sip or tube) N2 feeding*)) OR TI (((nasogastric or gastrostomy or jejunostomy) N2 tube*)) OR AB (((nasogastric or gastrostomy or jejunostomy) N2 tube*))

S9 TI (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteral feed*)) OR AB (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteral feed*)) OR TI (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteric feed*)) OR AB (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteric feed*)) OR TI (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteral intake*)) OR AB (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteral intake*))

S10 TI (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteric intake*)) OR AB (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteric intake*)) OR TI (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteral nutrition)) OR AB (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteral nutrition)) OR TI (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteric nutrition)) OR AB (((advanc* or aggressive* or delay* or early or fast or full or increas* or minimal or progress* or prolonged or rapid* or routine* or speed* or slow* or volume*) N3 enteric nutrition))

S11 TI (((aggressive* or fast or rapid* or slow* or speed*) N3 feed*)) OR AB (((aggressive* or fast or rapid* or slow* or speed*) N3 feed*)) OR TI (((aggressive* or fast or rapid* or slow* or speed*) N3 volume*)) OR AB (((aggressive* or fast or rapid* or slow* or speed*) N3 volume*)) OR TI trophic feeding OR AB trophic feeding* OR TI (((gut or gastrointestinal) N2 priming)) OR AB (((gut or gastrointestinal) N2 priming))

S12 S7 OR S8 OR S9 OR S10 OR S11

S13 S6 AND S12

S14 (MH "Double-Blind Studies")

S15 (MH "Single-Blind Studies")

S16 (MH "Random Assignment")

S17 (MH "Pretest-Posttest Design")

S18 (MH "Cluster Sample")

S19 TI (randomized or randomised) OR AB random* OR TI trial

S20 MH "sample size" AND AB ((assigned or allocated or control))

S21 MH placebos

S22 PT randomised controlled trial OR AB control W5 group OR MH "crossover design" OR MH "comparative studies" OR AB cluster W3 RCT

S23 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22

S24 S13 AND S23

S25 (MH "Parenteral Nutrition/AE")

S26 (MH "Enterocolitis, Necrotizing/CO/ET/EP/PC")

S27 (MH "Infection/EP")

S28 TI (((prevent* or risk*) N3 necrotising enterocolitis)) OR AB (((prevent* or risk*) N3 necrotising enterocolitis)) OR TI (((prevent* or risk*) N3 necrotizing enterocolitis)) OR AB (((prevent* or risk*) N3 necrotizing enterocolitis))

S29 S25 OR S26 OR S27 OR S28

S30 S6 AND S23 AND S29

S31 S24 OR S30

View Results (1,062)

Embase via Ovid

Search date 19 October 2020

Database: Embase <1974 to 2020 Week 42>

1 Newborn/

2 Prematurity/

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

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

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

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

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

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

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

10 infan$.ti,ab.

11 (baby or babies).ti,ab.

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

13 Enteric Nutrition/

14 ((enteral or enteric) adj2 (nutrition or feed$)).ti,ab.

15 ((oral or sip or tube) adj2 feeding$).ti,ab.

16 ((nasogastric or gastrostomy or jejunostomy) adj2 tube$).ti,ab.

17 ((advanc$ or aggressive$ or delay$ or early or fast or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteral feed$).ti,ab.

18 ((advanc$ or aggressive$ or delay$ or early or fast or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteric feed$).ti,ab.

19 ((advanc$ or aggressive$ or delay$ or early or fast or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteral nutrition).ti,ab.

20 ((advanc$ or aggressive$ or delay$ or early or fast or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteric nutrition).ti,ab.

21 ((advanc$ or aggressive$ or delay$ or early or fast or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteral intake).ti,ab.

22 ((advanc$ or aggressive$ or delay$ or early or fast or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteric intake).ti,ab.

23 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 feed$).ti,ab.

24 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 volume$).ti,ab.

25 trophic feeding$.ti,ab.

26 ((gut or gastrointestinal) adj2 priming).ti,ab.

27 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 12 and 27

29 Randomized controlled trial/

30 Controlled clinical study/

31 Random$.ti,ab.

32 randomization/

33 intermethod comparison/

34 placebo.ti,ab.

35 (compare or compared or comparison).ti.

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

37 (open adj label).ti,ab.

38 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

39 double blind procedure/

40 parallel group$1.ti,ab.

41 (crossover or cross over).ti,ab.

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

43 (assigned or allocated).ti,ab.

44 (controlled adj7 (study or design or trial)).ti,ab.

45 (volunteer or volunteers).ti,ab.

47 trial.ti.

48 or/29-47

49 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

50 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

51 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

52 (Systematic review not (trial or study)).ti.

53 (nonrandom$ not random$).ti,ab.

54 "Random field$".ti,ab.

55 (random cluster adj3 sampl$).ti,ab.

56 (review.ab. and review.pt.) not trial.ti.

57 "we searched".ab. and (review.ti. or review.pt.)

58 "update review".ab.

59 (databases adj4 searched).ab.

60 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

61 Animal experiment/ not (human experiment/ or human/)

62 or/49-61

63 48 not 62

64 28 and 63

65 Parenteral Nutrition/

66 complication/

67 safety/ or patient safety/

68 (adverse$ adj2 (effect$ or event$ or impact$ or outcome$)).ti,ab.

69 (complication$ or risk$ or safe or safely or safer or safety or sequaela or side effect$ or tolerated or toxicities or toxicity).ti,ab. (5056731)

70 65 and (66 or 67 or 68 or 69)

71 Necrotizing Enterocolitis/co, ep, et, pc [Complication, Epidemiology, Etiology, Prevention]

72 ((prevent$ or risk$) adj3 necrotising enterocolitis).ti,ab.

73 ((prevent$ or risk$) adj3 necrotizing enterocolitis).ti,ab.

74 Infection/ep [Epidemiology]

75 70 or 71 or 72 or 73 or 74

76 12 and 63 and 75

77 64 or 76

Maternity and infant Care Via Ovid

Search date 19 October 2020

Database: Maternity & Infant Care Database (MIDIRS) <1971 to August 2020>

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

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

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

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

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

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

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

8 infan$.ti,ab.

9 (baby or babies).ti,ab.

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

11 (Infant - premature or Infant - very low birth weight or Infant - newborn).de.

12 10 or 11

13 Enteral nutrition.de.

14 ((enteral or enteric) adj2 (nutrition or feed$)).ti,ab.

15 ((oral or sip or tube) adj2 feeding$).ti,ab.

16 ((nasogastric or gastrostomy or jejunostomy) adj2 tube$).ti,ab.

17 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteral feed$).ti,ab.

18 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteric feed$).ti,ab.

19 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteral intake$).ti,ab.

20 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteric intake$).ti,ab.

21 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteral nutrition).ti,ab.

22 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteric nutrition).ti,ab.

23 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 feed$).ti,ab.

24 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 volume$).ti,ab.

25 trophic feeding$.ti,ab.

26 ((gut or gastrointestinal) adj2 priming).ti,ab.

27 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 12 and 27

29 limit 28 to randomised controlled trial

30 Parenteral nutrition.de.

31 Enterocolitis - necrotizing.de.

32 (adverse$ adj2 (effect$ or event$ or impact$ or outcome$)).ti,ab.

33 (complication$ or risk$ or safe or safely or safer or safety or sequaela or side effect$ or tolerated or toxicities or toxicity).ti,ab.

34 Complications.de.

35 safety.de.

36 (30 or 31) and (32 or 33 or 34 or 35)

37 ((prevent$ or risk$) adj3 necrotising enterocolitis).ti,ab.

38 ((prevent$ or risk$) adj3 necrotizing enterocolitis).ti,ab.

39 36 or 37 or 38

40 limit 39 to randomised controlled trial

41 29 or 40

MEDLINE via Ovid

Search date 19 October 2020

Database: Ovid MEDLINE(R) ALL <1946 to October 16, 2020>

1 exp Infant, Newborn/

2 Premature Birth/

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

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

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

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

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

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

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

10 infan$.ti,ab.

11 (baby or babies).ti,ab.

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

13 Enteral Nutrition/

14 ((enteral or enteric) adj2 (nutrition or feed$)).ti,ab.

15 ((oral or sip or tube) adj2 feeding$).ti,ab.

16 ((nasogastric or gastrostomy or jejunostomy) adj2 tube$).ti,ab.

17 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteral feed$).ti,ab.

18 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteric feed$).ti,ab.

19 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteral intake$).ti,ab.

20 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteric intake$).ti,ab.

21 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteral nutrition).ti,ab.

22 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed$ or slow$ or volume$) adj3 enteric nutrition).ti,ab.

23 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 feed$).ti,ab.

24 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 volume$).ti,ab.

25 trophic feeding$.ti,ab.

26 ((gut or gastrointestinal) adj2 priming).ti,ab.

27 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 12 and 27

29 Parenteral Nutrition/ae [Adverse Effects]

30 Enterocolitis, Necrotizing/ep, et, pc [Epidemiology, Etiology, Prevention & Control]

31 ((prevent$ or risk$) adj3 necrotising enterocolitis).ti,ab.

32 ((prevent$ or risk$) adj3 necrotizing enterocolitis).ti,ab.

33 Infection/ep [Epidemiology]

34 29 or 30 or 31 or 32 or 33

35 12 and 34

36 28 or 35

37 randomized controlled trial.pt.

38 controlled clinical trial.pt.

39 randomized.ab.

40 placebo.ab.

41 drug therapy.fs.

42 randomly.ab.

43 trial.ab.

44 groups.ab.

45 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46 exp animals/ not humans.sh.

47 45 not 46

48 36 and 47

Trials Registers

ClinicalTrials.gov

Search one – Enteral feeding restricted to interventional studies about children aged birth to 17

Search two – Enterocolitis, necrotizing restricted to infants, interventional studies

WHO ICTRP

Search one – enteral nutrition

Search two – necrotizing enterocolitis

Appendix 2. 'Risk of bias' tool

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

For each included study, we categorised the method used to generate the allocation sequence as:

1. low risk (any truly random process, e.g. random number table; computer random number generator);
2. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk.

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

For each included study, we categorised the method used to conceal the allocation sequence as:

1. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
3. unclear risk.

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

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

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

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

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

1. low risk for outcome assessors;
2. high risk for outcome assessors; or
3. unclear risk for outcome assessors.

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

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we reincluded missing data in the analyses. We categorised the methods as:

1. low risk (less than 20% missing data);
2. high risk (20% or greater missing data); or
3. unclear risk.

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

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

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

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

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

1. low risk;
2. high risk; or
3. unclear risk.

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

HISTORY

Protocol first published: Issue 3, 2020
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

VW, JB, BC, and WM screened and appraised reports identified in the search, extracted and analysed data from included studies and drafted the review.

SO and WM arbitrated inclusion and data extraction disagreements.

All authors drafted the final review.

DECLARATIONS OF INTEREST

VW: none.

JB: none.

BC: none.

SO and WM are the co-investigators for the "Fluids exclusively enteral from day one in premature infants" trial (ISRCTN89654042).

WM is Cochrane Neonatal co-coordinating editor.

Core editorial and administrative support for this review has been provided by a grant from The Gerber Foundation. The Gerber Foundation is a separately endowed, private foundation, independent from the Gerber Products Company. The grantor has no input on the content of the review or the editorial process (see Sources of support).

SOURCES OF SUPPORT

Internal sources

- Centre for Reviews and Dissemination, University of York, UK

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.
- National Institute for Health Research (NIHR), UK

  This report is independent research funded by a UK NIHR Cochrane Programme Grant (16/114/03). The views expressed in this publication are those of the review authors and are not necessarily those of the National Health Service, the NIHR, or the UK Department of Health.
- The Gerber Foundation, USA

  Editorial support for this review, as part of a suite of preterm nutrition reviews, has been provided by a grant from The Gerber Foundation. The Gerber Foundation is a separately endowed, private, 501(c)(3) foundation not related to Gerber Products Company in any way.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. In the protocol (Walsh 2020), we stated a primary outcome of growth measured by "in hospital rate of weight gain (g/kg/day) until term equivalent". Only two studies reported this outcome, with Chetry 2014 reporting the result as the median and Nangia 2019 only reporting the mean with no standard deviations. The outcome of weight gain is an important outcome when comparing preterm feeding. All studies reported days to regain birth weight, and we decided to include this outcome in post hoc analyses.
2. The definition of growth restriction in Sanghvi 2013 (z-score at discharge) differed from our prespecified definition (z-score at term). We made a consensus post hoc decision to include the data based on the investigators' definition (Analysis 1.1).
3. The definitions of feed intolerance used in the included trials did not specify the duration of enteral feed interruption (Bora 2017; Nangia 2019; Sanghvi 2013). We made a consensus post hoc decision to include the data based on the investigators' definitions (Analysis 1.3).

INDEX TERMS

Medical Subject Headings (MeSH)

Body Weight; Enteral Nutrition [adverse effects] [*methods]; Enterocolitis, Necrotizing [epidemiology] [etiology]; Fluid Therapy; Infant Formula; Infant, Premature [*growth & development]; Infant, Very Low Birth Weight [*growth & development]; Milk, Human; Randomized Controlled Trials as Topic; Weight Gain

MeSH check words

Humans; Infant, Newborn