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Watson J, McGuire W

Watson J, McGuire W.
Responsive versus scheduled feeding for preterm infants.
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD005255.
DOI: 10.1002/14651858.CD005255.pub5.

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TABLE OF CONTENTS

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[Intervention Review]

Responsive versus scheduled feeding for preterm infants

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2016.

Citation: Watson J, McGuire W. Responsive versus scheduled feeding for preterm infants. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD005255. DOI: 10.1002/14651858.CD005255.pub5.

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ABSTRACT

Background

Feeding preterm infants in response to their hunger and satiation cues (responsive, cue-based, or infant-led feeding) rather than at scheduled intervals might enhance infants' and parents' experience and satisfaction, help in the establishment of independent oral feeding, increase nutrient intake and growth rates, and allow earlier hospital discharge.

Objectives

To assess the effect of a policy of feeding preterm infants on a responsive basis versus feeding prescribed volumes at scheduled intervals on growth rates, levels of parent satisfaction, and time to hospital discharge.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review group to search the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 1), MEDLINE via PubMed (1966 to 17 February 2016), Embase (1980 to 17 February 2016), and CINAHL (1982 to 17 February 2016). We also searched clinical trials' databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs that compared a policy of feeding preterm infants on a responsive basis versus feeding at scheduled intervals.

Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and undertook data extraction independently. We analysed the treatment effects in the individual trials and reported the risk ratio and risk difference for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We used a fixed-effect model in meta-analyses and explored the potential causes of heterogeneity in sensitivity analyses. We assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We found nine eligible RCTs including 593 infants in total. These trials compared responsive with scheduled interval regimens in preterm infants in the transition phase from intragastric tube to oral feeding. The trials were generally small and contained various methodological weaknesses including lack of blinding and incomplete assessment of all randomised participants. Meta-analyses, although limited by data quality and availability, suggest that responsive feeding results in slightly slower rates of weight gain (MD −1.36, 95%

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CI −2.44 to −0.29 g/kg/day), and provide some evidence that responsive feeding reduces the time taken for infants to transition from enteral tube to oral feeding (MD −5.53, 95% CI −6.80 to −4.25 days). GRADE assessments indicated low quality of evidence. The importance of this finding is uncertain as the trials did not find a strong or consistent effect on the duration of hospitalisation. None of the included trials reported any parent, caregiver, or staff views.

Authors' conclusions

Overall, the data do not provide strong or consistent evidence that responsive feeding affects important outcomes for preterm infants or their families. Some (low quality) evidence exists that preterm infants fed in response to feeding and satiation cues achieve full oral feeding earlier than infants fed prescribed volumes at scheduled intervals. This finding should be interpreted cautiously because of methodological weaknesses in the included trials. A large RCT would be needed to confirm this finding and to determine if responsive feeding of preterm infants affects other important outcomes.

PLAIN LANGUAGE SUMMARY

Responsive feeding versus scheduled feeding for preterm infants

Review question: Does a policy of feeding preterm infants on a responsive basis compared to feeding prescribed volumes at scheduled intervals improve growth, length of hospital stay and parent satisfaction?

Background: Feeding preterm infants in response to their hunger and satiation cues (responsive, cue-based, or infant-led feeding) rather than at scheduled intervals might enhance infants' and parents' experience and satisfaction, help in the establishment of independent oral feeding, increase nutrient intake and growth rates, and allow earlier hospital discharge.

Study characteristics: We searched for all available evidence up to January 2016. We found nine eligible randomised controlled trials (including a total of 593 infants) that examined whether feeding preterm infants in response to their own feeding and satiation cues (sometimes called 'demand' feeding) is better than feeding set volumes of milk at predefined intervals. These trials compared responsive with scheduled interval regimens in preterm infants in the transition phase from intragastric tube to oral feeding.

Results: Although the trials were generally small and most had some methodological weaknesses, analysis suggests that responsive feeding results in slightly slower rates of weight gain and reduces the time taken for infants to transition from enteral tube to oral feeding. The quality of this evidence is low, and the importance of this finding is uncertain as the trials did not find a strong or consistent effect on the length of hospitalisation. None of the included trials reported any parent, caregiver, or staff views.

Conclusions: This Cochrane review does not provide strong or consistent evidence that responsive feeding improves outcomes for preterm infants or their families. Responsive feeding might help infants transition more quickly to oral feeding, but more randomised controlled trials would be needed to confirm this finding.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Patient or population: preterm infants
Setting: healthcare facility
Intervention: responsive feeding
Comparison: scheduled interval feeding

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with scheduled interval feeding	Risk with Responsive			
Weight change during study period (g/kg/day)	Comparator	Mean weight change during study period in the intervention group was 1.36 g/kg/day lower (95% CI 0.29 to 2.44 lower)	305 (4 studies)	⊕⊕◯◯ Low[a,b]	3 trials that did not find any evidence of effect on the rate of weight gain did not provide data for inclusion in meta-analyses
Time to establishment of full oral feeds (after trial entry)	Comparator	Mean time to establishment of full oral feeds (after trial entry) in the intervention group was 5.5 days shorter (4.2 to 6.8 days shorter)	167 (2 studies)	⊕⊕◯◯ Low[a,b]	Most trials did not report this outcome.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

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

[a] Risk of bias - lack of blinding in trials
[b] Publication and reporting bias probable

BACKGROUND

Description of the condition

The frequency of feeding and volume of milk intake of healthy term infants is generally dictated by the infant's appetite. Term infants exhibit feeding and satiation cues and adjust their volume of intake to compensate for differences in the nutrient density of various milks (Fomon 1969; Fomon 1975). In contrast, enteral feeds for preterm infants are usually given as prescribed volumes at scheduled intervals (Siddell 1994). Some evidence exists that preterm infants are also able to self-regulate their intake (Horton 1952; Tyson 1983). Furthermore, while feeding cues may be more difficult to detect in preterm infants, they may be sufficiently evident for a parent or caregiver to recognise and respond to (Ross 2002). Caregivers and parents can use infants' physiological and behavioural channels of communication to inform their feeding decisions and actions. Although studies have shown that responsive (cue-based) feeding is feasible for preterm infants, the adoption of responsive feeding has however been constrained by the "schedule- and volume-driven culture" in many neonatal units (Shaker 2013).

Description of the intervention

Alternatives to a strict scheduled interval feeding regimen for preterm infants have been described (Crosson 2004). These strategies aim to respond to infant feeding and satiation cues and are particularly relevant to infants who are in the transition phase from gastric tube feeding to oral feeding (either breast, bottle, or cup-feeding) (Davanzo 2014). At this stage (from about 32 to 36 weeks' postmenstrual age), preterm infants are usually developing sustained alert activity and a coordinated suck-swallow-breathe pattern (Bu'Lock 1990; Holditch-Davis 2003).

Responsive (cue-based or infant-led, and previously often referred to as 'demand') feeding is a co-regulated approach (Crosson 2004). The enteral feeding process starts when the caregiver recognises infant cues that indicate readiness to feed and ends when the infant demonstrates satiation. The infant, therefore, determines the timing, duration, and volume of intake. In modifications of responsive feeding, caregivers may preset a maximum permitted duration of inactivity or sleep (generally up to five or six hours) between feeds or a maximum (upper limit) volume of intake. This strategy is more suited to infants who are receiving gastric tube feeds or who are fed orally from a bottle or cup. It is much more difficult to determine when the target volume of intake has been reached in breast-fed infants.

Infant cues

An infant's ability to feed well is closely related to the caregiver's ability to understand and respond to the infant's behavioural communication. Common cues include quiet wakefulness, hand-to-mouth gestures, and finger or fist sucking. Crying is a late feeding cue; mouthing, tongue-poking, arm waving, kicking, stretching, bicycling legs, and grunting are often exhibited before crying. Waiting for an infant to cry before feeding may mean caregivers have already missed key initial feeding cues and can lead to poor latching (in breast-fed infants), and gulping and air-swallowing. For a preterm infant, crying for feeds wastes effort and energy as well as raising stress levels at such a vulnerable developmental stage. If the quality of a feed takes priority over the quantity ingested, feeding skills may develop pleasurably and at the infant's own pace, enhancing the parents' experience of nurturing their child and satisfaction of neonatal care (Puntis 2006; Kirk 2007; Shaker 2013; Briere 2014).

How the intervention might work

Responsive feeding may be considered a part of an integrated approach to providing 'developmental care' for preterm infants. Infants are seen as individuals in their own right and caregivers are guided by the needs of the infant. The Cochrane review of other components of developmental care found some evidence that interventions such as minimising unnecessary exposure to external stimuli and clustering of care activities increase nutrient intake and rates of growth, and decreases the length of hospital stay (Symington 2006). Allowing preterm infants to dictate the timing and duration of enteral feeding may result in longer rest periods between some feeds, promote infant-determined sleep and wake patterns that reduce unnecessary energy expenditure, and increase growth rates (McCain 2003). It is also possible that allowing the infant to determine the pattern of enteral feeding will help in the development of organised behaviour states and the earlier establishment of full oral feeding, a key criterion for hospital discharge for preterm infants (AAP 2008; Rose 2008). This may be particularly relevant for infants and their mothers transitioning to exclusive breastfeeding. Responsive feeding for preterm infants in neonatal intensive care is now recommended as a method to increase the duration of breastfeeding in the United Nations Children's Emergency Fund (UNICEF) Baby-Friendly Hospital Initiative "Ten steps to successful breastfeeding" (Nyqvist 2013). There may be other benefits for the family and caregivers, principally allowing parents to feel more directly involved with their infant's care and increasing their confidence and ability to recognise and respond to their infant's needs during their hospital stay and beyond. Enhanced parental satisfaction is a key quality indicator in measuring the effectiveness of family-centred care in neonatal services (Nair 2014).

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Why it is important to do this review

Responsive feeding might help in the establishment of independent oral feeding, allow earlier hospital discharge, and enhance parent experience. Reducing length of hospital stay has a direct effect on hospital costs and may also decrease cot occupancy in neonatal units, thus reducing the need for inter-hospital transfer of women and infants. Potential adverse effects of responsive feeding for preterm infants are also recognised. These mainly relate to whether such a regimen can guarantee metabolic stability, particularly normoglycaemia, in this vulnerable group. Even at the point of discharge from hospital, some preterm infants are known to be susceptible to hypoglycaemia if a scheduled enteral feed is omitted or delayed (Hume 1999; Mola-Schenzle 2015). There is concern that repeated or prolonged episodes of hypoglycaemia may impair longer term growth and development (Duvanel 1999). There may be more acute problems relating to gastro-intestinal immaturity, such as feeding intolerance and a higher risk of aspiration of gastric contents into the lungs, as well as concerns that allowing unrestrained volumes of enteral intake may increase the risk of gastro-oesophageal reflux or feed intolerance.

OBJECTIVES

To assess the effect of a policy of feeding preterm infants on a responsive basis versus feeding prescribed volumes at scheduled intervals on growth rates, levels of parent satisfaction, and time to hospital discharge.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs. Cluster-RCTs where the unit of randomisation was a group of infants (for example, all infants cared for in a participating neonatal unit) were also eligible for inclusion. We excluded cross-over studies that assessed the use of two feeding strategies in the same infant as this design would not permit a meaningful assessment of the effect of the intervention on the important outcomes for this Cochrane review (growth rates and time to hospital discharge). Studies published as abstracts were eligible for inclusion only if assessment of study quality was possible and if other criteria for inclusion were fulfilled. We contacted the authors of studies published as abstracts for further information if required.

Types of participants

Preterm infants (less than 37 weeks' gestation) at least partially enterally fed. Participating infants may have been fed with formula or human breast milk (or both) via any enteral route including tube, bottle, breast, or cup.

Types of interventions

- Responsive feeding: The enteral feed starts in response to the infant's feeding cues and ends when the infant exhibits satiation cues. We accepted trials that assessed modifications or variations of responsive feeding such as: (i) the feed starts in response to the infant's cues but ends when a prescribed volume of intake is reached; (ii) the infant may be fed if he or she remains asleep beyond a predefined interval for assessing cues.
- Scheduled interval feeding: Feeds are given at scheduled intervals without regard to the infant's sleep or wake status. Orally fed infants who are asleep are awakened to feed or fed via an enteral feeding tube if unable to be awoken sufficiently.

The infants in the comparison groups in each trial must have received the same type(s) of milk. We excluded trials where the type of milk is a co-intervention (unless as part of a factorial design in the RCT).

Any feeding cues used in individual trials were acceptable provided these were defined a priori. Trials that used the response to non-nutritive sucking on a pacifier as a tool for assessing readiness to feed in the intervention group were eligible for inclusion. However, we planned to interpret the findings of these trials with caution since the Cochrane review of non-nutritive sucking found evidence that this intervention improves bottle-feeding performance and is associated with a statistically significant decrease in length of hospital stay for preterm infants (Pinelli 2005). We did not specify a minimum trial duration as a primary eligibility criterion. However, we planned only to include growth data in meta-analyses from trials that allocated the intervention for a sufficient period (at least one week) to allow measurable effects on growth.

Types of outcome measures

Primary outcomes

1. Growth: (a) weight gain (g/day or g/kg/day); linear growth (mm/week); head circumference (mm/week); skinfold thickness (mm/week) during the trial period. (b) Proportion of infants who remain below the 10th percentile for the index population's distribution of weight, height, or head circumference when assessed at hospital discharge, 40 weeks' postmenstrual age, during infancy, and beyond.
2. Duration of hospital admission: postmenstrual age or chronological age (days from birth or from trial enrolment), or both, to discharge to home from hospital.

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3. Measures of parental satisfaction using validated assessment tools.

Secondary outcomes

1. Age (postmenstrual age or days from birth) at establishment of full oral feeding (independent of intragastric tube feeding).
2. Nutrient intake during trial period: mean volume of milk and intake of energy or protein (per kg/day).
3. Duration of breastfeeding (time from start of trial until infant stops receiving any human breast milk) and breastfeeding prevalence (any and exclusive) on discharge and at three and six months post term.
4. Milk aspiration: consistent clinical history and chest x-ray findings.
5. Hypoglycaemia requiring treatment with unscheduled enteral supplement or intravenous fluids or glucagon.
6. Feed intolerance defined as a requirement to cease enteral feeds and commence parenteral nutrition.
7. Neurodevelopmental outcomes at more than 12 months' corrected age measured using validated assessment tools such as Bayley Scales of Infant Development, and classifications of disability including auditory and visual disability. We defined the composite outcome 'severe neurodevelopmental disability' as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient < 70), auditory and visual impairment.

Search methods for identification of studies

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

Electronic searches

We used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group search strategy for specialized register).
We conducted a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 7) in the Cochrane Library; MEDLINE via PubMed (1996 to current); Embase (1980 to current); and CINAHL (1982 to current) using the following search terms: (Feeding Behavior OR Sucking Behavior OR Cues OR oral feeding OR demand feeding OR semi-demand feeding OR self-regulatory feeding OR ad libitum OR feeding cues OR satiation), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We did not apply language restrictions.
We searched clinical trials' registries for ongoing or recently completed trials (ClinicalTrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictrp/search/en/; and the ISRCTN Registry (www.isrctn.com)).

Searching other resources

We examined the references in all studies identified as potentially relevant.
We searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2014), the European Society for Paediatric Research (1995 to 2014), the UK Royal College of Paediatrics and Child Health (2000 to 2015), and the Perinatal Society of Australia and New Zealand (2000 to 2014). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the trial authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group (neonatal.cochrane.org/).

Selection of studies

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

Data extraction and management

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

Assessment of risk of bias in included studies

We used the criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of any included trials. Additional information from the trial authors was requested to clarify methodology and results as necessary. We evaluated and reported the following issues in the 'Risk of bias' tables:

1. Sequence generation: we categorised the method used to generate the allocation sequence as:
   i) low risk: any random process e.g. random number table; computer random number generator;
   ii) high risk: any non-random process e.g. odd or even date of birth; patient case-record number;
   iii) unclear.
2. Allocation concealment: we categorised the method used to conceal the allocation sequence as:
   i) low risk: e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes;

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ii) high risk: open random allocation; unsealed or non-opaque envelopes; alternation; date of birth;
iii) unclear.

3. Blinding: we assessed blinding of participants, clinicians and caregivers, and outcome assessors separately for different outcomes and categorised the methods as:
i) low risk;
ii) high risk;
iii) unclear.

4. Incomplete outcome data: we described the completeness of data including attrition and exclusions from the analysis for each outcome and any reasons for attrition or exclusion where reported. We assessed whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised completeness as:
i) low risk: less than 10% data missing;
ii) high risk: 10% or more data missing;
iii) unclear.

Measures of treatment effect

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

Unit of analysis issues

The unit of analysis was the participating infant in individual RCTs and the neonatal unit (or sub-unit) for cluster-RCTs.

Dealing with missing data

We requested additional data from the trial investigators if data on important outcomes were missing or reported unclearly.

Assessment of heterogeneity

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 describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. If moderate or high heterogeneity was detected (I^2 statistic > 50%), we explored the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments) in sensitivity analyses.

Data synthesis

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

Quality of evidence

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

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

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

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

Two review authors assessed independently the quality of the evidence found for outcomes identified as critical or important for clinical decision making (growth, time to oral feeding).
In cases where we considered risk of bias arising from inadequate concealment of allocation, poorly randomised assignment, incomplete follow-up or inadequate blinding of outcome assessment reduced our confidence in the effect estimates, we downgraded the quality of evidence accordingly (Guyatt 2011b). We evaluated consistency on the basis of similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria, including measurement of heterogeneity (I^2). We downgraded the quality of evidence when inconsistency across study results was large and unexplained (i.e. some studies suggested important benefit, and others no effect or harm with no explanation) (Guyatt 2011c). We assessed precision accordingly with the 95% confidence interval (CI) around the pooled estimation (Guyatt 2011d). When trials were conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness (Guyatt 2011e).
We entered data (pooled estimates of effects and corresponding 95% CIs) and explicit judgements for each of the above aspects assessed into the Guideline Development Tool, the software used

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to create 'Summary of findings' (SoF) tables (GRADEpro 2008). We explained our assessment of study characteristics in footnotes in the SoF table.

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we planned to undertake additional subgroup analyses of:

1. trials where all participating infants were exclusively fed from the breast versus trials where participants were formula-fed;
2. trials where the infants' responses to non-nutritive sucking were used to assess hunger versus trials that did not included assessments using non-nutritive sucking.

RESULTS

Description of studies

Results of the search

We included nine trials and excluded six studies (Figure 1).

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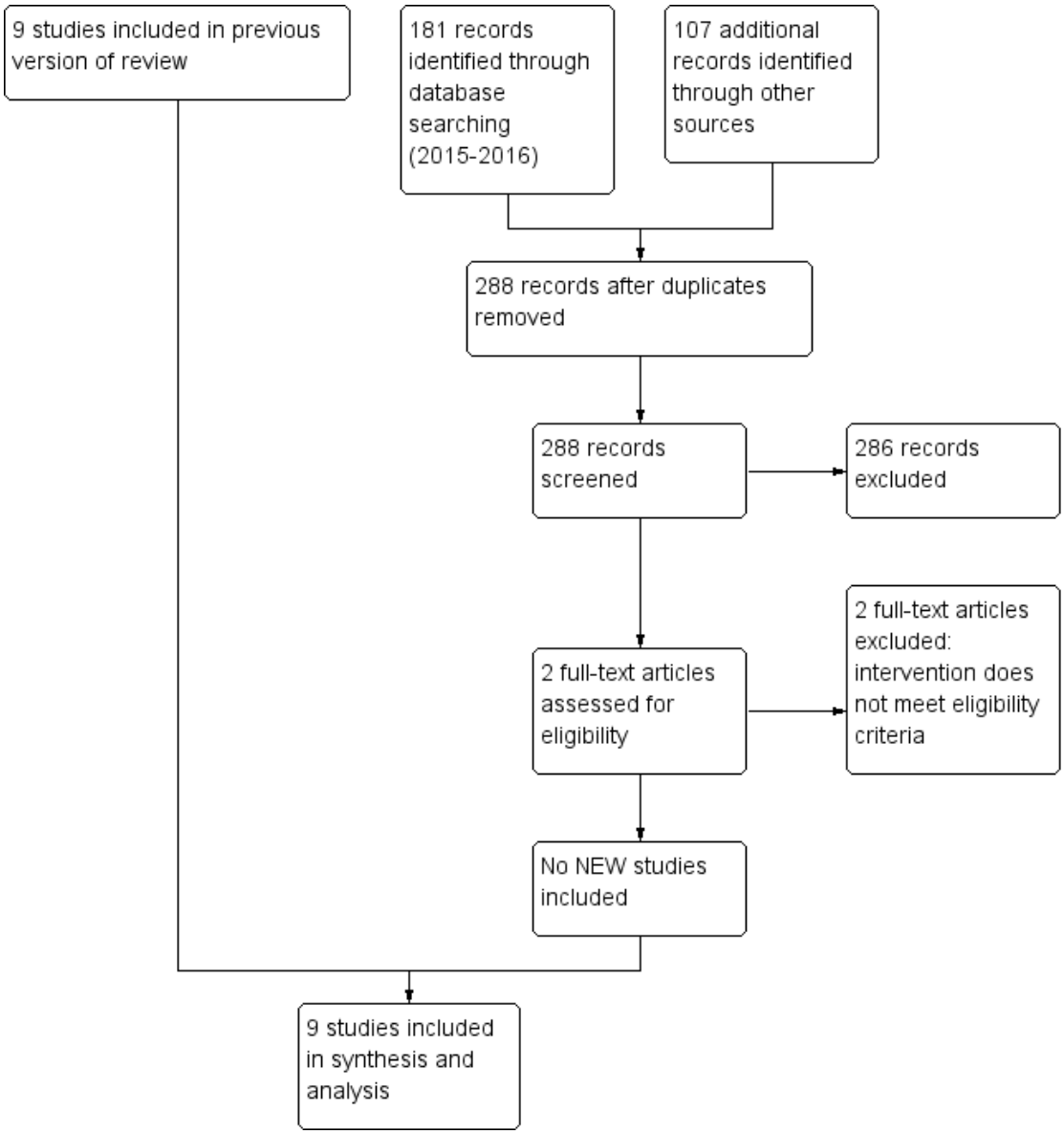
Figure 1. Study flow diagram: review update



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Included studies

These are described in detail in the Characteristics of included studies section (Collinge 1982; Saunders 1991; Waber 1998; Pridham 1999; McCain 2001; Pridham 2001; Kansas 2004; Puckett 2008; McCain 2012).

Participants

All of the included trials were undertaken since 1980 by investigators attached to neonatal units in North America. The trials were small: 582 infants in total participated. The participants in all of the trials were clinically stable preterm infants who were fully enterally fed and at transition from intragastric tube feeds to oral feeds (generally between 32 and 36 weeks' postmenstrual age). Most trials excluded infants who were small for gestational age at birth and infants with congenital anomalies or gastrointestinal or neurological problems. The balance of oral versus tube feeding at enrolment differed between trials. One trial enrolled infants at the start of transition to oral feeding when infants were mainly fed via an intragastric tube (McCain 2001). In the other trials, infants were enrolled later in the transition phase when they were receiving most of their feeds orally. In six trials, intragastric feeding tubes were removed when infants were allocated to the intervention group (Collinge 1982; Waber 1998; Pridham 1999; Pridham 2001; Kansas 2004; Puckett 2008). The most recently reported trial recruited only preterm infants with a history of bronchopulmonary dysplasia, defined as receipt of supplemental oxygen therapy at 28 days postnatally (McCain 2012). The mean gestational age of infants in this trial was 25 weeks, and infants were recruited at an average postmenstrual age of 35 to 36 weeks.

Interventions

Most trials described responsive feeding as allowing the infant to feed orally in response to cues such as crying, sucking on fingers/pacifier, or rooting. Feeding was ceased only in response to satiation cues, such as sleep or failure to maintain sucking. In three trials, infants who did not demonstrate feeding cues within five hours were aroused to feed orally or given a prescribed volume of milk via an intragastric tube (Saunders 1991; Waber 1998; Puckett 2008). In two trials, the infant's readiness to feed was assessed every three hours by the response to non-nutritive sucking (McCain 2001; McCain 2012). Oral feeds were stopped when the infant stopped sucking or fell asleep. If the minimum prescribed amount was not taken the infants received a prescribed volume via the intragastric tube.

Scheduled interval feeding was generally defined as regular feeding either orally or via an intragastric feeding tube at three- to four-hourly intervals to achieve a prescribed intake. The target volume of intake in the trials varied from 100 to 160 mL/kg/day. In all of the trials the infants in the intervention and control groups received the same type(s) of milk. Most trial protocols permitted infants to receive either breast milk or formula milk or a mixture of these. One trial recruited only formula milk-fed infants (Saunders 1991).

Outcomes

The trials assessed only short-term outcomes, principally volume and energy intake, and growth parameters (usually weight) during the study period. The duration of study period was less than a week in six of the trials. In the other three trials the intervention was continued until the infants were assessed as being ready for discharge home, typically 10 to 14 days (Kansas 2004; Puckett 2008; McCain 2012).

Excluded studies

We excluded Horton 1952, Anderson 1990, Chang 2004, and Kirk 2007, and have listed the reasons for exclusion in the Characteristics of excluded studies section. Anderson 1990 assessed the effect of a range of nipples for bottle feeding and for non-nutritive sucking but did not specifically assess responsive feeding versus scheduled interval feeding. Chang 2004 described a randomised cross-over study in which 11 preterm infants were randomly allocated to receive responsive feeds for 48 hours followed by scheduled interval feeds for 48 hours or vice versa. As this study design does not allow the collection of meaningful data on growth and time to hospital discharge - the primary outcomes of this Cochrane review - the trial was not considered eligible for inclusion. Horton 1952 reported a case series of low birth weight infants who received demand oral feeds. Kirk 2007 reported an epoch-comparison of outcomes for infants demand-fed versus scheduled interval-fed controls.

Risk of bias in included studies

The methodological quality of the included trials varied (Figure 2).

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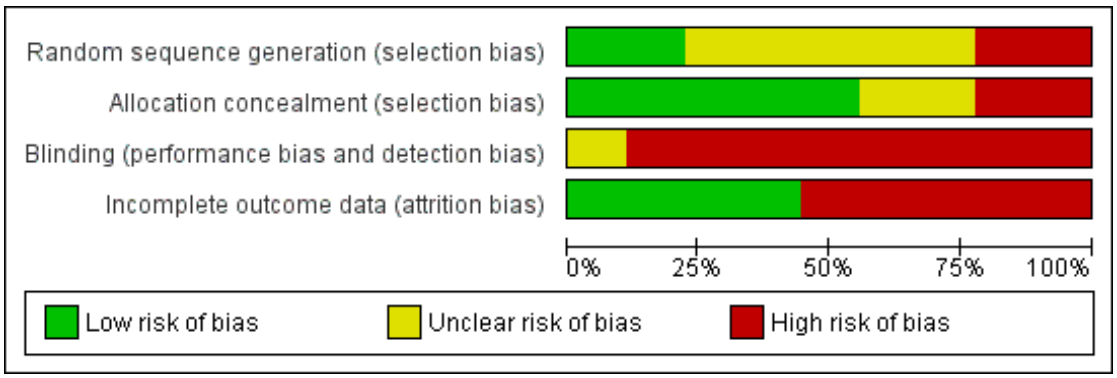
Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



Allocation

Seven reports described a randomisation procedure that is likely to have achieved satisfactory allocation concealment.

Blinding

Due to the nature of the intervention, parents and caregivers were not blinded in any of the trials. It is unlikely that outcome assessment was blinded in any of the trials as the primary outcomes (nutrient intake and weight gain) were assessed by caregivers.

Incomplete outcome data

Follow-up was complete or near-complete in seven of the trials, but not in Pridham 1999 and Pridham 2001 where 46% of enrolled infants were discharged home before completing the prespecified five days' study period. Outcome data were not recorded for these infants.

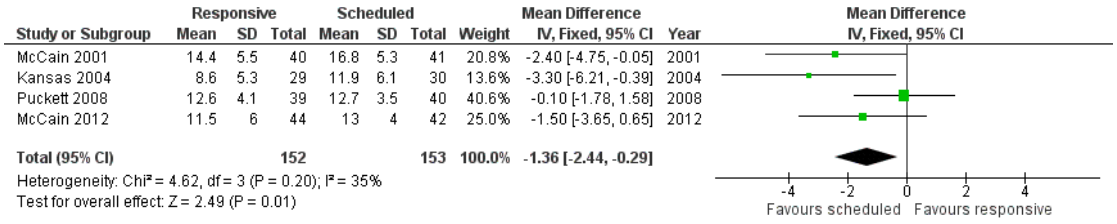
Effects of interventions

See: **Summary of findings for the main comparison** Responsive versus scheduled feeding for preterm infants

Growth

Eight trials reported data on this outcome. Four trials (305 infants) reported rates of weight gain during the trial period (McCain 2001; Kansas 2004; Puckett 2008; McCain 2012). Meta-analysis showed a statistically significantly lower rate of weight gain in the responsive feeding group: MD −1.36, 95% CI −2.44 to −0.29 g/kg/day; four trials, 305 participants; I^2 = 35%; Analysis 1.1; Figure 3.

Figure 3. Forest plot of comparison: 1 Responsive versus scheduled interval feeding, outcome: 1.1 Growth: weight change during study period (g/kg/day).



Three other trials reported that there was not a statistically significant difference in the rate of weight gain during the trial period, but the duration of intervention in these trials was less than one week (Saunders 1991; Pridham 1999; Pridham 2001). Waber 1998 reported that the average daily weight gain in the

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intervention group was 26.4 g versus 34.1 g in the control group. The trial authors did not state whether this difference was statistically significant. Standard deviation (SD) values were not reported. We sought but did not obtain further data from the trial authors.

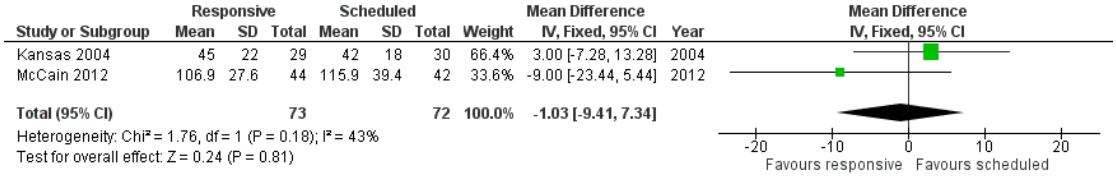
None of the trials provided data on linear growth, head circumference growth, or changes in skinfold thickness during the trial period.

None of the trials reported any data on longer-term growth parameters.

Duration of hospital admission

Seven trials reported data on this outcome. McCain 2012 and Kansas 2004 individually, and a meta-analysis of data from both trials, did not find a statistically significant difference in the total length of hospitalisation (Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: 1 Responsive versus scheduled interval feeding, outcome: 1.2 Duration of hospital admission (days).



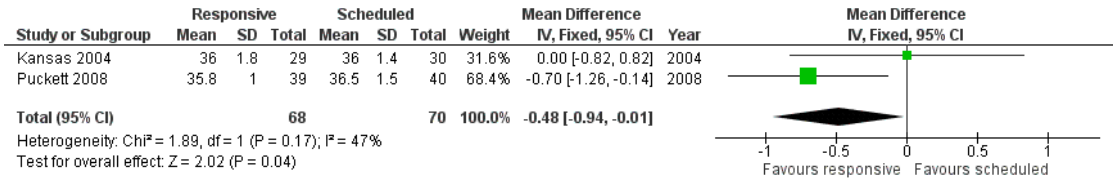
Waber 1998 reported that the duration of hospital stay was 31 days in the intervention group versus 33 days in the control group. The trial authors did not state whether this difference was statistically significant, and did not report SD values. We sought but did not obtain further data from the trial authors.

Pridham 1999 and Pridham 2001 stated that there was not a statistically significant difference in the duration of hospital stay following randomisation (numerical data not available).

Postmenstrual age at discharge

Two trials (138 infants) reported postmenstrual age at discharge (Kansas 2004; Puckett 2008). Meta-analysis showed a borderline statistically significantly lower age at discharge in infants in the intervention group: MD −0.48, 95% CI −0.94 to −0.01 weeks; two trials, 138 participants; I^2 = 49%; Analysis 1.3; Figure 5.

Figure 5. Forest plot of comparison: 1 Responsive versus scheduled interval feeding, outcome: 1.3 Postmenstrual age at discharge (weeks).



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Time from trial enrolment until hospital discharge

Collinge 1982 reported a statistically significant difference in the number of days from study enrolment until infants were ready for hospital discharge: 2.7 days versus 8.9 days. The trial authors did not report or provide SD values.

Saunders 1991 did not report age at hospital discharge but did state that there was not a statistically significant difference in the duration of hospital stay following randomisation: 7.2 days in the intervention group versus 8.4 days in the control group. The trial authors did not report the SD values. Further data are no longer available from the trial authors.

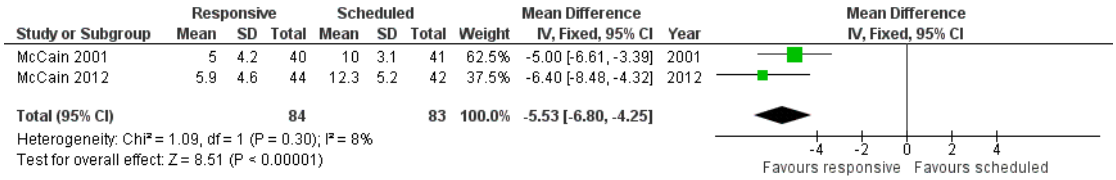
Parental satisfaction

This outcome was not reported in any of the included trials.

Time to establishment of full oral feeds

Two trials reported data on this outcome. McCain 2001 and McCain 2012 , and a meta-analysis of data from both trials, showed a statistically significant reduction in the time taken to achieve full oral feeding after trial entry: MD −5.53, 95% CI −6.80 to −4.25 days; two trials, 167 participants; I^2 = 8%; Analysis 1.4; Figure 6).

Figure 6. Forest plot of comparison: 1 Responsive versus scheduled interval feeding, outcome: 1.3 Time to establishment of full oral feeds (after trial entry).



Collinge 1982 reported that the intervention group achieved establishment of full oral feeds independently of tube feeding earlier than the control group but did not comment on statistical significance or provide data to assess statistical significance.

Nutrient intake during trial period

Five trials reported on this outcome. Four trials reported daily volume of intake during the study period for those infants who were not breast-fed, since it was not possible to measure nutrient intake of breastfeeding infants (Collinge 1982; McCain 2001; Kansas 2004; Puckett 2008). Meta-analysis showed a borderline statistically significantly lower volume in infants fed responsively: MD −5.75, 95% CI −12.12 to 0.62 mL/kg/day; four trials, 208 participants; Analysis 1.5.

Three trials reported daily energy intake during the study period (McCain 2001; Kansas 2004; McCain 2012). Meta-analysis did not show a statistically significant difference: MD 0.52, 95% CI −2.33 to 3.37 kCal/kg/day; three trials, 208 participants; Analysis 1.5.

Pridham 1999 and Pridham 2001 both reported that energy intake was lower in the responsive group than the control group during the five days' study period. The reports do not state whether this difference was statistically significant.

Waber 1998 reported lower average levels of fluid, energy, and protein intake in the responsive group but did not state whether any of these differences were statistically significant. SD values were not reported and are not available from the trial authors.

Duration of breast-feeding

This outcome was not reported in any of the included trials.

Milk aspiration

This outcome was not reported in any of the included trials.

Hypoglycaemia

This outcome was not reported in any of the included trials.

Feed intolerance

This outcome was not reported in any of the included trials.

Neurodevelopmental outcomes

This outcome was not reported in any of the included trials.

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Subgroup analyses

1. Trials where all participating infants were exclusively fed from the breast: none of the trials belonged to this subgroup.
2. Trials where the infants' responses to non-nutritive sucking were used to assess hunger: two trials belonged to this subgroup (McCain 2001; McCain 2012). See above for trial description and findings.

DISCUSSION

Summary of main results

Nine small RCTs including a total of 593 infants met the inclusion criteria of this Cochrane review. The data from these trials do not provide strong evidence that responsive feeding affects important outcomes for preterm infants or their families. Meta-analyses suggest that responsive feeding results in slightly lower levels of milk intake and rates of weight gain, but these findings should be interpreted cautiously because of methodological weaknesses in the included trials. Although the trials provide some evidence that responsive feeding reduces the time taken for infants to transition from enteral tube to oral feeding - a key criterion for determining readiness for discharge from hospital - the importance of this finding is uncertain as the trials did not find a strong or consistent effect on the duration of hospitalisation.

Overall completeness and applicability of evidence

All but one of the included trials assessed the rate of weight gain but none reported data on change in length or head circumference. The short duration of the intervention and follow-up (less than a week) of many of the trials is unlikely to have allowed detection of substantial effects on growth. Meta-analysis of data from four trials which assessed weight gain for longer than one week (up to between 10 and 14 days) indicated that infants fed responsively gained weight slightly more slowly, gaining about 1.4 g/kg/day fewer than scheduled interval-fed infants. This effect on the rate of weight gain is consistent with a meta-analysis of data from the four trials which showed that responsive feeding resulted in a borderline statistically significantly lower volume of milk intake of about 6 mL/kg/day.

Three included trials reported that responsive feeding shortened the duration of the transition phase from tube to full oral feeds. Meta-analysis of data from two trials that recruited infants at the start of the transition to the oral feeding phase indicated that responsive feeding allows infants to establish oral feeding about five days earlier. However, the findings from these trials should be interpreted cautiously because the trial authors used non-nutritive sucking on a pacifier to assess readiness to feed and some evidence exists that non-nutritive sucking itself shortens the transition from tube to oral feeds for preterm infants (Pinelli 2005).

Two trials reported that infants fed in response to feeding cues were discharged home several days earlier than infants in the scheduled interval feeding group (Collinge 1982; Puckett 2008). The other trials did not confirm this finding. Meta-analysis of the effect of the intervention on the duration of hospital stay was limited because the included trials reported this outcome in different ways (total duration of hospital stay from birth, duration of stay post-randomisation, postmenstrual age at hospital discharge), and because some trial reports did not provide sufficient data.

Acceptability and impact

It is unclear whether any of these marginal effects have any longer-term impacts or are of substantial importance to infants and families. None of the trials assessed any measures of parental (or staff) satisfaction with the intervention package. It is perhaps surprising that investigators have not assessed systematically the views of parents and caregivers given that the intervention is part of an integrated approach to providing 'developmental care' for preterm infants, an ethos that is relationship-based rather than protocol-driven and task-orientated (Symington 2006). Similarly, none of the trials reported any data on breastfeeding outcomes or on potential harms or adverse consequences of responsive feeding, including metabolic instability, milk aspiration, or feed intolerance.

Applicability

Most included trials recruited very stable preterm infants without ongoing respiratory problems or other concerns. One trial recruited extremely preterm infants with evidence of bronchopulmonary dysplasia but these infants were enrolled when in a stable phase, typically at around 35 weeks' postmenstrual age (McCain 2012). The data therefore are most applicable to preterm infants who are at the transition phase from enteral tube feeding to oral feeding and who are stable and well.

All included trials were undertaken in neonatal care centres in North America. Although the findings are likely to be applicable to care practices in countries with similar types of perinatal health care services, it is much less clear how applicable this evidence is to care practices in low- and middle-income countries. In resource-limited settings, lower levels of staff availability (lower nurse:infant ratios) reduces the time available for assessment of individual infants' feeding cues. Conversely, if mothers rather than staff are the primary caregivers in resource-limited healthcare settings then responsive feeding regimens may be more feasible and practical, provided mothers are able, or are trained and supported to be able, to recognise feeding cues in preterm infants.

Quality of the evidence

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The GRADE assessment of quality of evidence for key outcomes was low because of possible publication or reporting bias (trials that did not show evidence of effect did not report numerical data for inclusion in meta-analyses) as well as concerns about the methodological rigour of the included trials. Although most trials used randomisation and allocation methods to prevent selection bias, none concealed the method of feeding from parents, caregivers, assessors, or investigators (Figure 2). This may potentially have resulted in performance or detection bias and knowledge of the feeding method may have affected other parental or clinical decisions, including those related to the timing of hospital discharge. Attrition bias was likely to have affected outcome estimates in two trials where almost half of all enrolled infants were discharged home before completing the study. Outcome data for inclusion in intention-to-treat (ITT) analyses were not reported or available for these infants (Pridham 1999; Pridham 2001).

Potential biases in the review process

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

AUTHORS' CONCLUSIONS

Implications for practice

The currently available data are not sufficient to determine whether responsive feeding versus feeding prescribed enteral volumes at scheduled intervals improves important outcomes for preterm infants. Although some limited evidence exists that responsive feeding allows earlier attainment of full oral feeding, these findings should be interpreted and applied cautiously because of methodological weaknesses in the included trials.

Implications for research

There is a need for a large pragmatic RCT to assess whether responsive feeding (versus scheduled interval feeding) improves important clinical outcomes for preterm infants and their families. Such a trial should probably focus first on those infants at the transition from enteral tube to oral feeding. The involvement of parent and infant support and advocacy groups in the trial design would inform the selection of the most relevant outcomes, including those related to parental satisfaction. Trials could also assess resource issues, such as the use of staff time to undertake assessments and feeding, as these may have implications for an economic analysis if responsive feeding is to have clinical benefits.

ACKNOWLEDGEMENTS

We thank Kerri Turner, Gail McCain, Karen Pridham, Barbara Puckett, Rebecca Saunders, and Brenda Waber for kindly providing further information regarding their trials (Saunders 1991; Waber 1998; Pridham 1999; McCain 2001; Pridham 2001; Kansas 2004; Puckett 2008).

We thank Felicia McCormick and Karen Tosh for contributions to a previous version of this Cochrane review (McCormick 2010).

The Cochrane Neonatal Review Group has been funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN267200603418C.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Collinge 1982

Methods	RCT
Participants	36 preterm infants, birth weight less than 2500 g and appropriate for gestational age. Infants were recruited when they weighed at least 1800 g and were fully enterally fed and receiving at least 1 feed per day by gavage via an intragastric feeding tube. Breast milk-fed and formula milk-fed infants (or mixed) participated in the trial. Formula-fed infants received either standard term formula or nutrient-enriched 'preterm' formula, or both. There is no indication in the report that the choice of type of formula was associated with the feeding regime allocation. Infants with severe gastrointestinal or neurological problems were not eligible to participate
Interventions	Intervention (N = 18): responsive feeding, defined as "allowing the infant to feed as frequently as (s)he wishes, and to take as much as desired at each feeding". Infants were fed (orally or via a gastric feeding tube) in response to crying, sucking on fingers or pacifier, activity and rooting. The trial report does not state which satiation cues were assessed. Control (N = 18) received prescribed volumes of milk (up to 160 mL/kg/day) either orally or via a feeding tube at 3- to 4-hourly intervals
Outcomes	*Volume of intake during trial period. Total number of feeds per day, and number of feeds given via gastric feeding tube per day. Time from randomisation to discharge from hospital.
Notes	Setting: Montreal Children's Hospital, Canada. 1981 to 1982. *Further information on methodology and results (SD) were not available from the trial investigators. SD imputed from Puckett 2008 trial with most similar sample size and effect size in the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

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Collinge 1982 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: can't tell.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.

Kansas 2004

Methods	RCT
Participants	59 preterm infants (born before 33 weeks' gestational age) who were able to take at least half of their enteral feeds orally from a nipple (either bottle or breast)
Interventions	Intervention (N = 29): at randomisation, enteral feeding tubes were removed and infants were then fed in response to cues (no maximum or minimum feeding volume or interval) via a nipple. Control (N = 30): scheduled interval feeding with gavage feeding if infant did not ingest prescribed volume from nipple
Outcomes	Days (from birth) to discharge to home from hospital. Daily weight gain. Average daily volume of milk intake.
Notes	Setting: duPont Hospital for Children, Philadelphia, USA. 2003. Reported in abstract form only. Further information on methodology kindly provided by trial investigators

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.

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McCain 2001

Methods	RCT
Participants	81 preterm infants of postmenstrual age between 32 to 34 weeks who were fully enterally fed. Infants with severe periventricular haemorrhage, congenital anomalies, or gastrointestinal or neurological problems were not eligible to participate. Infants were fed fortified human milk or commercial formula at 105 to 130 kcal/kg/day as per nursery standard of care. The infants had indwelling nasogastric tubes until they reached full oral feeding
Interventions	Intervention group (N = 40): responsive ('semi-demand') feeding - infants received 10 minutes of non-nutritive sucking every 3 hours to assess wakefulness and behavioural state. Infants who were wakeful were offered an oral feed. If the infant was not sufficiently awake, (s)he was left to sleep a further 30 minutes and the process was repeated. If the infant continued to sleep at that stage, (s)he was given a gavage feed of the full prescribed volume. Feeds were stopped when the infant stopped sucking or fell asleep or demonstrated clinical instability. If the minimum prescribed amount was not taken the infants were supplemented by gavage. Control infants (N = 41) received prescribed volumes of milk either orally or via a feeding-tube at 3-hourly intervals. Feeding duration was restricted to a maximum of 30 minutes. 1 infant in the control group was transferred to another hospital after completing the study protocol. The 'age at discharge home' is not known
Outcomes	Time taken from start of study to achieve full oral feeding. Rate of weight gain during transition from enteral tube to oral feeds
Notes	Setting: neonatal units affiliated to University of Cincinnati, Ohio, USA, late 1990s

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pre-prepared random sequence unknown to investigators (personal communication from principal investigator)
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes (personal communication from principal investigator)
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up: yes.

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McCain 2012

Methods	RCT
Participants	96 preterm infants with bronchopulmonary dysplasia (supplemental oxygen at 28 days) Mean gestational age at birth: 25 weeks.
Interventions	Intervention group (N = 48): responsive ('semi-demand') feeding regulated by using infant behavioural and cardiorespiratory signs, which determined the frequency, length and volume of nipple/oral feeds. Infants offered three hourly feeds if awake Control (N = 48): standard care increased in number of nipple to gavage feeds per day
Outcomes	Time to achieve oral feeds. Length of hospital stay. *Weight gain.
Notes	Setting: neonatal intensive care unit at Jackson Memorial Hospital, Miami, Florida (2006 to 2009) Nurses were trained to recognise infants behaviour states and researchers carried out reliability tests on a weekly basis for the first 3 months of the trial *Mean PMA at study entry: 35 to 36 weeks. Estimated mean weight at study entry of 2 kg used to impute growth rates as g/kg/day (from reported g/day)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated (with minimisation for birth weight and gestational age strata, sex, and ethnicity)
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	High risk	86 infants completed the trial protocol: 4 experimental group and 6 control group infants withdrawn due to feeding intolerance, sepsis, tachypnoea or maternal request (data not reported or available for inclusion in ITT re-analyses)

Pridham 1999

Methods	RCT
Participants	150 infants less than 35 weeks' gestational age at birth and appropriate weight for gestational age were enrolled and randomised. Infants were enrolled in the trial when taking at least 80% of enteral feeds directly from a nipple (either breast or bottle), at which point tube feeding was ceased and all feeds were offered by nipple. Most infants received standard formula milk. As part of a factorial trial design, some infants were randomly allocated to receive calorie-enriched formula milk

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Pridham 1999 (*Continued*)

Interventions	Intervention (N = 94): responsive feeding initiated in response to infant hunger cues and terminated in response to infant satiation. Control (N = 56): prescribed feeding at 4-hourly intervals.
Outcomes	Weight change, volume intake and calorie intake during the study period (5 days)
Notes	Setting: Level III neonatal unit in Wisconsin, USA. 1992 to 1994 Further information on methodology kindly provided by trial investigators

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Blinding of randomisation: yes.
Allocation concealment (selection bias)	Low risk	Blinding of randomisation: yes.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	High risk	Failure to complete full 5 days' study period: 69 of the 150 (46%) enrolled infants were discharged home before completing the 5 days' study period and no outcome data were presented for these infants

Pridham 2001

Methods	RCT
Participants	49 infants less than 35 weeks' gestational age at birth and appropriate weight for gestational age. Infants were enrolled in the trial when taking at least 80% of enteral feeds directly from a nipple (either breast or bottle), at which point tube feeding was ceased and all feeds were offered by nipple. Most participating infants received breast milk
Interventions	Intervention (N = 25): responsive, initiated in response to infant hunger cues and terminated in response to infant satiation. Control (N = 24): prescribed feeding at 3-hourly intervals.
Outcomes	Weight change, volume intake and calorie intake during the study period (5 days)
Notes	Setting: Level III neonatal unit in Wisconsin, USA. 1990 to 1993 Further information on methodology kindly provided by trial investigators

Risk of bias

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Pridham 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blinding of randomisation: yes.
Allocation concealment (selection bias)	Low risk	Blinding of randomisation: yes.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	High risk	Failure to complete full 5 days' study period: 23 of the 49 (47%) enrolled infants were discharged home before completing the 5 days' study period and no outcome data were presented for these infants

Puckett 2008

Methods	RCT
Participants	80 infants (including healthy moderately preterm infants and previously ventilated convalescing extremely low birth weight infants including those remaining oxygen dependent) with current weight > 1500 g and tolerating full oral feeds were randomised at 32 to 36 weeks' postmenstrual age Infants being mechanically ventilated and those with congenital abnormalities, major gastrointestinal surgery or severe intraventricular haemorrhage were excluded
Interventions	Intervention (N = 40): at study entry, gavage feeds were discontinued and infants fed orally on demand in response to hunger cues (crying, hand-to-mouth activity, finger/fist/pacifier sucking, rooting, persistently 'unsettled' following a diaper change or repositioning). 5-hour limit between feeds - if no cues the infant was woken for feeding Control (N = 40): continued standard scheduled (schedule not reported) gavage and bottle feeding Both groups: "Breastfeedings were allowed as per parent's request". Type(s) of formula used were not reported. Modes of interim feeding other than gavage and bottle not reported
Outcomes	Weight gain (g/kg/day), length of stay following enrolment, menstrual age at discharge, adverse events (apnoea and bradycardia) during feeding, number of cues per feed in the intervention group, and resource utilisation using nurse-infant ratios
Notes	Setting: Level III neonatal unit in Saskatoon, Saskatchewan, Canada. 2001 to 2003. Data collected until hospital discharge are reported. Outcome data were presented for 79 of the 80 randomised infants (data missing for 1 infant in the intervention group)
Risk of bias	

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Puckett 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Coin toss with subsequent infant allocated to opposite group
Allocation concealment (selection bias)	High risk	Coin toss with subsequent infant allocated to opposite group
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete follow-up: outcome data were presented for 79 of the 80 randomised infants (data missing for 1 infant in the intervention group)

Saunders 1991

Methods	RCT
Participants	29 preterm infants without major neurological or gastrointestinal disorders. Infants were enrolled when their weight was greater than 1500 g and they were fully enterally fed with formula milk
Interventions	Intervention (N = 15): responsive to hunger cues (crying, finger/fist sucking, rooting, persistently 'unsettled' following a diaper change or re-positioning). 5-hour limit between feeds Control (N = 14): prescribed feeding of set volumes at 3-hourly intervals to achieve at least 120 mL/kg/day intake Infants in either group who failed to take adequate amounts orally for two consecutive feeds were fed a prescribed volume (to achieve a daily intake of 120 mL/kg/day) via an intragastric feeding tube for the next feed
Outcomes	Rate of weight gain during the 6-day trial period. Length of hospitalisation. Saunders 1991 did not collect data on nutrient intake (personal communication from principal investigator)
Notes	Setting: Level III neonatal unit at the Women's Hospital, Greensboro, North Carolina, USA We gratefully received further information on methodology and results from the trial investigator

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.

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Saunders 1991 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 infants were withdrawn from the study, 1 for withdrawal of parental consent, 1 because of infection, and 1 because of hypoglycaemia. It is not stated to which feeding group these infants had been randomly allocated

Waber 1998

Methods	Quasi-RCT
Participants	13 preterm infants born before 34 weeks' gestation, and appropriate for gestational age. Weight greater than 1500 g, postmenstrual age greater than 32 weeks at time of enrolment and fully enterally fed
Interventions	Intervention (N = 5): 'Demand' oral feeding (intragastric tubes removed) in response to hunger cues (crying, finger/hand/pacifier sucking, rooting, 'unsettled'). The feeds were regarded as complete and ceased in response to infant satiation cues (refusal to suck and sleep). If infant did not demonstrate hunger cues within 5 hours of a previous feed, then infant gently aroused to a "feeding alert state". Control (N = 5): prescribed feeding of set volumes at 3- to 4-hourly intervals to achieve intake of 140 to 150 mL/kg/day
Outcomes	Growth: average weight gain during trial period. Average volume of intake, and calorie and protein intake during trial period. No SDs given.
Notes	Setting: The Children's Regional Hospital, Camden, New Jersey, USA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Coin-toss" for alternate infants, with allocation to opposite group for subsequently-enrolled infant
Allocation concealment (selection bias)	High risk	"Coin-toss" for alternate infants, with allocation to opposite group for subsequently-enrolled infant
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention: no. Blinding of outcome measurement: no.

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Waber 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	10 of 13 enrolled infants completed the trial, but the reasons for withdrawal/drop-out were not stated

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

Study	Reason for exclusion
Anderson 1990	This trial assessed the effect of a range of nipples for bottle feeding and for non-nutritive sucking but did not specifically assess ad libitum or demand/semi-demand feeding versus scheduled interval feeding. This study was reported only as a book chapter
Chang 2004	This is a two period cross-over study comparing ad libitum feeding with 3-hourly scheduled interval feeding. Because this study design does not allow the collection of meaningful data on growth and time to hospital discharge, the primary outcomes of this Cochrane review, the trial was not considered eligible for inclusion
Horton 1952	This is an observational study of demand feeding in low birth weight infants
Kirk 2007	This is an epoch-comparison study using a historic control cohort
Pickler 2015	This is a protocol for a RCT of "patterned" feeding for preterm infants, providing "tactile experiences [...] with feeding to train and build neuronal networks supportive of normal infant feeding experience". This intervention does not meet the inclusion criteria for this review
Tubbs-Cooley 2015	This is a preliminary report of data from Pickler 2015.

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DATA AND ANALYSES

Comparison 1. Responsive versus scheduled interval feeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth: weight change during study period (g/kg/day)	4	305	Mean Difference (IV, Fixed, 95% CI)	-1.36 [-2.44, -0.29]
2 Duration of hospital admission (days)	2	145	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-9.41, 7.34]
3 Postmenstrual age at discharge (weeks)	2	138	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.94, -0.01]
4 Time to establishment of full oral feeds (after trial entry)	2	167	Mean Difference (IV, Fixed, 95% CI)	-5.53 [-6.80, -4.25]
5 Nutrient intake during trial period (non breast-fed infants only)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Volume of milk (mL/kg/day)	4	208	Mean Difference (IV, Fixed, 95% CI)	-5.75 [-12.12, 0.62]
5.2 Energy intake (kCal/kg/day)	3	208	Mean Difference (IV, Fixed, 95% CI)	0.52 [-2.33, 3.37]

Analysis 1.1. Comparison 1 Responsive versus scheduled interval feeding, Outcome 1 Growth: weight change during study period (g/kg/day).

Review: Responsive versus scheduled feeding for preterm infants

Comparison: 1 Responsive versus scheduled interval feeding

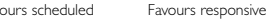
Outcome: 1 Growth: weight change during study period (g/kg/day)

Study or subgroup	Responsive N	Mean(SD)	Scheduled N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McCain 2001	40	14.4 (5.5)	41	16.8 (5.3)		20.8 %	-2.40 [-4.75, -0.05]
Kansas 2004	29	8.6 (5.3)	30	11.9 (6.1)		13.6 %	-3.30 [-6.21, -0.39]
Puckett 2008	39	12.6 (4.1)	40	12.7 (3.5)		40.6 %	-0.10 [-1.78, 1.58]
McCain 2012	44	11.5 (6)	42	13 (4)		25.0 %	-1.50 [-3.65, 0.65]
Total (95% CI)	**152**		**153**			**100.0 %**	**-1.36 [-2.44, -0.29]**

Heterogeneity: Chi² = 4.62, df = 3 (P = 0.20); I² =35%

Test for overall effect: Z = 2.49 (P = 0.013)

Test for subgroup differences: Not applicable



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Analysis 1.2. Comparison 1 Responsive versus scheduled interval feeding, Outcome 2 Duration of hospital admission (days).

Review: Responsive versus scheduled feeding for preterm infants

Comparison: 1 Responsive versus scheduled interval feeding

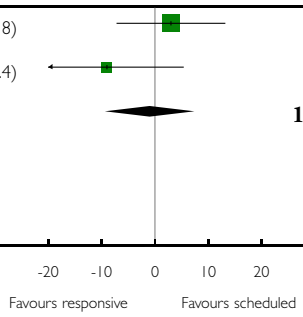
Outcome: 2 Duration of hospital admission (days)

Study or subgroup	Responsive N	Mean(SD)	Scheduled N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kansas 2004	29	45 (22)	30	42 (18)		66.4 %	3.00 [-7.28, 13.28]
McCain 2012	44	106.9 (27.6)	42	115.9 (39.4)		33.6 %	-9.00 [-23.44, 5.44]
Total (95% CI)	**73**		**72**			**100.0 %**	**-1.03 [-9.41, 7.34]**

Heterogeneity: Chi^2 = 1.76, df = 1 (P = 0.18); I^2 =43%

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable



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Analysis 1.3. Comparison 1 Responsive versus scheduled interval feeding, Outcome 3 Postmenstrual age at discharge (weeks).

Review: Responsive versus scheduled feeding for preterm infants

Comparison: 1 Responsive versus scheduled interval feeding

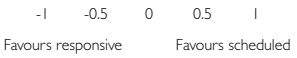
Outcome: 3 Postmenstrual age at discharge (weeks)

Study or subgroup	Responsive N	Mean(SD)	Scheduled N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kansas 2004	29	36 (1.8)	30	36 (1.4)		31.6 %	0.0 [-0.82, 0.82]
Puckett 2008	39	35.8 (1)	40	36.5 (1.5)		68.4 %	-0.70 [-1.26, -0.14]
Total (95% CI)	**68**		**70**			**100.0 %**	**-0.48 [-0.94, -0.01]**

Heterogeneity: Chi² = 1.89, df = 1 (P = 0.17); I² =47%

Test for overall effect: Z = 2.02 (P = 0.043)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Responsive versus scheduled interval feeding, Outcome 4 Time to establishment of full oral feeds (after trial entry).

Review: Responsive versus scheduled feeding for preterm infants

Comparison: 1 Responsive versus scheduled interval feeding

Outcome: 4 Time to establishment of full oral feeds (after trial entry)

Study or subgroup	Responsive N	Mean(SD)	Scheduled N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McCain 2001	40	5 (4.2)	41	10 (3.1)		62.5 %	-5.00 [-6.61, -3.39]
McCain 2012	44	5.9 (4.6)	42	12.3 (5.2)		37.5 %	-6.40 [-8.48, -4.32]
Total (95% CI)	**84**		**83**			**100.0 %**	**-5.53 [-6.80, -4.25]**

Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² =8%

Test for overall effect: Z = 8.51 (P < 0.00001)

Test for subgroup differences: Not applicable

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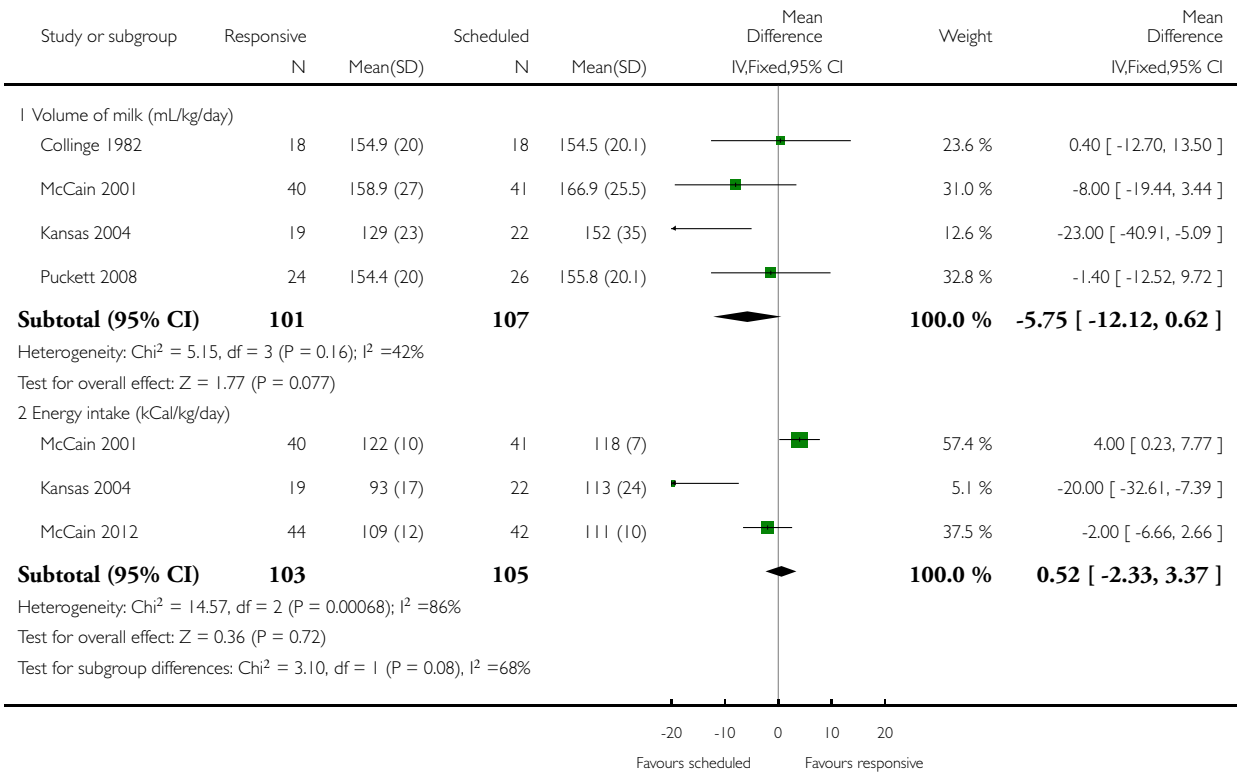
Analysis 1.5. Comparison 1 Responsive versus scheduled interval feeding, Outcome 5 Nutrient intake during trial period (non breast-fed infants only).

Review: Responsive versus scheduled feeding for preterm infants

Comparison: 1 Responsive versus scheduled interval feeding

Outcome: 5 Nutrient intake during trial period (non breast-fed infants only)



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APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))
Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)
CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Last assessed as up-to-date: 27 June 2016.

Date	Event	Description
27 July 2016	New citation required but conclusions have not changed	Search updated, but no new trials found.
27 June 2016	New search has been performed	Summary of findings table included; updated search.

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 3, 2006

Date	Event	Description
25 April 2015	New citation required but conclusions have not changed	We modified the title and terminology to reflect current infant- and family-centred approaches to care (type of feeding now described as "responsive" rather than "ad libitum or demand/semi-demand") The updated search identified one new study for inclusion (McCain 2012).
25 April 2015	New search has been performed	This is an update of the Cochrane review "Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants" (McCormick 2010).

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(*Continued*)

24 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Julie Watson screened the title and abstract of all studies identified by the updated search strategy. William McGuire and Julie Watson screened the full text of the reports identified as of potential relevance, assessed the methodological quality of the included trials, extracted the relevant information and data, and completed the review update.

DECLARATIONS OF INTEREST

Julie Watson and William McGuire do not have any potential conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Hull York Medical School, and Centre for Reviews & Dissemination, University of York, UK.
- Faculty of Health and Wellbeing, Sheffield Hallam University, UK.

External sources

- UK National Institute of Health Research Grant (NIHR), UK.

This report is independent research funded by a UK NIHR Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the review authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

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

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

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INDEX TERMS

Medical Subject Headings (MeSH)

Enteral Nutrition [*methods; standards]; Hunger [*physiology]; Infant Nutritional Physiological Phenomena [*physiology]; Infant, Premature [*physiology]; Randomized Controlled Trials as Topic; Satiation [physiology]; Time Factors; Weight Gain

MeSH check words

Humans; Infant, Newborn

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