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TABLE OF CONTENTS

[Intervention Review]

Early additional food and fluids for healthy breastfed full-term infants

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ABSTRACT

Background

Health organisations recommend exclusive breastfeeding for six months. However, the addition of other fluids or foods before six months is common in many countries. Recently, research has suggested that introducing solid food at around four months of age while the baby continues to breastfeed is more protective against developing food allergies compared to exclusive breastfeeding for six months. Other studies have shown that the risks associated with non-exclusive breastfeeding are dependent on the type of additional food or fluid given. Given this background we felt it was important to update the previous version of this review to incorporate the latest findings from studies examining exclusive compared to non-exclusive breastfeeding.

Objectives

To assess the benefits and harms of additional food or fluid for full-term healthy breastfeeding infants and to examine the timing and type of additional food or fluid.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 March 2016) and reference lists of all relevant retrieved papers.

Selection criteria

Randomised or quasi-randomised controlled trials in infants under six months of age comparing exclusive breastfeeding versus breastfeeding with any additional food or fluids.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. Two review authors assessed the quality of the evidence using the GRADE approach.

Main results

We included 11 trials (2542 randomised infants/mothers). Nine trials (2226 analysed) provided data on outcomes of interest to this review. The variation in outcome measures and time points made it difficult to pool results from trials. Data could only be combined in a meta-analysis for one primary (breastfeeding duration) and one secondary (weight change) outcome. None of the trials reported on physiological jaundice. Infant mortality was only reported in one trial.

For the majority of older trials, the description of study methods was inadequate to assess the risk of bias. Most studies that we could assess showed a high risk of other biases and over half were at high risk of selection bias.

Providing breastfeeding infants with artifical milk, compared to exclusive breastfeeding, did not affect rates of breastfeeding at hospital discharge (risk ratio (RR) 1.02, 95% confidence interval (CI) 0.97 to 1.08; one trial, 100 infants; *low-quality evidence*). At three months, breastfeeding infants who were provided with artificial milk had higher rates of any breastfeeding compared to exclusively breastfeeding infants (RR 1.21, 95% CI 1.05 to 1.41; two trials, 137 infants; *low-quality evidence*). Infants who were given artifical milk in the first few days after birth before breastfeeding, had less "obvious or probable symptoms" of allergy compared to exclusively breastfeeding infants (RR 0.56, 95% CI 0.35 to 0.91; one trial, 207 infants; *very low-quality evidence*). No difference was found in maternal confidence when comparing non-exclusive breastfeeding infants who were provided with artificial milk with exclusive breastfeeding infants (mean difference (MD) 0.10, 95% CI -0.34 to 0.54; one study, 39 infants; *low-quality evidence*). Rates of breastfeeding were lower in the non-exclusive breastfeeding group compared to the exclusive breastfeeding group at four, eight, 12 (RR 0.68, 95% CI 0.53 to 0.87; one trial, 170 infants; *low-quality evidence)*, 16 and 20 weeks.

The addition of glucose water resulted in fewer episodes of hypoglycaemia (below 2.2 mmol/L) compared to the exclusive breastfeeding group, reported at 12 hours (RR 0.07, 95% CI 0.00 to 1.20; one trial, 170 infants; *very low-quality evidence*), but no significant difference at 24 hours (RR 1.57, 95% CI 0.27 to 9.17; one trial, 170 infants; *very low-quality evidence*). Weight loss was lower for infants who received additional glucose water (one trial, 170 infants) at six, 12, 24 and 48 hours of life (MD -32.50 g, 95% CI -52.09 to -12.91; *low-quality evidence)* compared to the exclusively breastfeeding infants but no difference between groups was observed at 72 hours of life (MD 3.00 g, 95% CI -20.83 to 26.83; *very low-quality evidence).* In another trial with the water and glucose water arms combined (one trial, 47 infants), we found no significant difference in weight loss between the additional fluid group and the exclusively breastfeeding group on either day three or day five (MD -1.03%, 95% CI -2.24 to 0.18; *very low-quality evidence*) and (MD -0.20%, 95% CI -0.86 to 0.46; *very low-quality evidence*).

Infant mortality was reported in one trial with no deaths occurring in either group (1162 infants). The early introduction of potentially allergenic foods, compared to exclusively breastfeeding, did not reduce the risk of "food allergy" to one or more of these foods between one to three years of age (RR 0.80, 95% CI 0.51 to 1.25; 1162 children), visible eczema at 12 months stratified by visible eczema at enrolment (RR 0.86, 95% CI 0.51 to 1.44; 284 children), or food protein-induced enterocolitis syndrome reactions (RR 2.00, 95% CI 0.18 to 22.04; 1303 children) (*all moderate-quality evidence).* Breastfeeding infants receiving additional foods from four months showed no difference in infant weight gain (g) from 16 to 26 weeks compared to exclusive breastfeeding to six months (MD -39.48, 95% CI -128.43 to 49.48; two trials, 260 children; *low-quality evidence*) or weight z-scores (MD -0.01, 95% CI -0.15 to 0.13; one trial, 100 children; *moderate-quality evidence*).

Authors' conclusions

We found no evidence of benefit to newborn infants on the duration of breastfeeding from the brief use of additional water or glucose water. The quality of the evidence on formula supplementation was insufficient to suggest a change in practice away from exclusive breastfeeding. For infants at four to six months, we found no evidence of benefit from additional foods nor any risks related to morbidity or weight change. The majority of studies showed high risk of other bias and most outcomes were based on low-quality evidence which meant that we were unable to fully assess the benefits or harms of supplementation or to determine the impact from timing and type of supplementation.

We found no evidence to disagree with the current international recommendation that healthy infants exclusively breastfeed for the first six months.

PLAIN LANGUAGE SUMMARY

Early additional food and fluids for healthy breastfed full-term infants

What is the issue?

Internationally, exclusive breastfeeding for the first six months of life is recommended but the practice of giving breastfeeding infants other fluids and/or foods before six months is common in many countries and communities.

Why is this important?

Given that many infants are not exclusively breastfeeding for six months it is important to examine the possible benefits or risks associated with giving breastfeeding infants liquids other than breastmilk or complementary food in the first six months after birth.

What evidence did we find?

This review includes 11 randomised controlled trials involving 2542 infants.

Giving babies small amounts of artificial milk for a few days after birth in addition to breastfeeding did not effect the number of infants with any breastfeeding at hospital discharge though did slightly increase the likelihood of any breastfeeding at three months of age. There was no difference in the level of maternal confidence between the groups. The use of artificial milk before breastfeeding had a slight protective effect against allergy symptoms at 18 months of age compared to exclusive breastfeeding, however the trial did not perform diagnostic challenges or other tests to confirm the allergy symptoms noticed and thus requires caution in interpretation.

The likelihood of infants continuing to breastfeed was higher in the exclusive breastfeeding group than the group provided with additional water or glucose water in the first few days after birth. There was no evidence of benefit related to glucose levels, temperature, weight loss to breastfeeding newborn infants who were given additional water or glucose water.

Breastfeeding infants receiving complementary foods at four to six months did not show reduced risk of food allergy, eczema, or food protein-induced enterocolitis syndrome reactions. There was no difference between the early complementary foods and the exclusive breastfeeding groups for the percentage of days of cough, congestion, nasal discharge and hoarseness, fever, iron deficiency or weight gain.

What does this mean?

This review did not find sufficient evidence for disagreement with the recommendation of the World Health Organization and other international health organisations that as a general policy exclusive breastfeeding, without additional foods or fluids, should be recommended for the first six months after birth.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Non-exclusive breastfeeding (artificial milk) versus exclusive breastfeeding

Patient or population: healthy breastfeeding full-term infants
Setting: hospital settings USA, Sweden and the Czech Republic
Intervention: non-exclusive breastfeeding infants (artificial milk)
Comparison: exclusive breastfeeding infants

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with exclusive breastfeeding infants	Risk with non-exclusive breastfeeding infants (artificial milk)				
Any breastfeeding at discharge	Study population		RR 1.02 (0.97 to 1.08)	100 (1 RCT)	⊕⊕◯◯ LOW [1,2,3]	
	980 per 1000	1000 per 1000 (951 to 1000)				
Any breastfeeding at 3 months	Study population		RR 1.21 (1.05 to 1.41)	137 (2 RCTs)	⊕⊕◯◯ LOW [1,2,4,5]	
	765 per 1000	925 per 1000 (803 to 1000)				
Infant morbidity - allergy symptoms - Infants with allergy symptoms at 18 months of age	Study population		RR 0.56 (0.35 to 0.91)	207 (1 RCT)	⊕◯◯◯ VERY LOW [5,7]	
	327 per 1000	183 per 1000 (114 to 297)				
Weight change						This outcome was not reported.

Maternal self-confidence Modified breastfeeding self-efficacy score at 1 week. Items rated on a scale from 1 ("Strongly Disagree") to 5 ("Strongly Agree"), with positive scores associated with increased breastfeeding self-efficacy	The mean maternal self-confidence was 3.9 units (SD 0.7) n = 20	The mean maternal self-confidence in the artificial milk group was 0.1 units higher on a 5-point scale (95% CI 0.34 lower to 0.54 higher)	-	39 (1 RCT)	⊕⊕◯◯ LOW [1,2,6]	Modified breastfeeding self-efficacy score at 1 week. Items rated on a scale from 1 ("Strongly Disagree") to 5 ("Strongly Agree") with higher scores associated with more breastfeeding self-efficacy

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

__CI:__ Confidence interval; __RR:__ Risk ratio

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

[1] Control group had low adherence to the study protocol (-1).
[2] We are unsure of the impact of the recruitment of only infants with greater than or equal to 5% weight loss as 5% is within normal expected range.
[3] Wide confidence intervals crossing the line of no effect and small sample size (-1).
[4] 1 trial had baseline imbalances in multiparity.
[5] Evidence based on small sample size (-1).
[6] Confidence intervals crossing the line of no difference and small sample size (-1).
[7] 1 trial with quasi-random sequence generation, baseline imbalances for family history of allergy, 1 infant was changed from its allocated group due to family history of allergy, unclear if exclusive breastfeeding group received water or colostrum in the first 48 hours, high number of outcome assessors working independently and diagnosis of allergy was based on clinical criteria with no diagnostic testing

BACKGROUND

Human milk for human babies is the biological norm. It has long been recognised as both the unequalled way of providing all the nutritional, immunological and psychological requirements that a healthy, term infant needs to thrive, and important to the health and well-being of the mother. Reviews of studies in both economically advantaged and disadvantaged settings have shown short-term and long-term risks to the child and to the mother from not breastfeeding (Chen 2004; Horta 2013a; Ip 2007; Kramer 2012; Leon-Cava 2002; Victora 2016).

Description of the condition

Exclusive breastfeeding is defined as an infant's consumption of human milk with no supplementation of any type, including no water, juice, non-human milk or foods, although medicines, vitamins and minerals are allowed (WHO 2008). A review of interventions in 42 developing countries estimated that exclusive breastfeeding for six months and continued breastfeeding for the first year of life could prevent 13% of the over 10 million deaths per annum of children less than five years old. Breastfeeding is identified as the single most important preventative intervention in saving such lives (Black 2013; Jones 2003). Compared to exclusive breastfeeding, the risks from partial or non-exclusive breastfeeding have been recognised for many years, including a higher rate of infant morbidity and mortality from diarrhoea and respiratory illness (Arifeen 2001; Brown 1989; Chantry 2006; Feachem 1984; Horta 2013b; Kramer 2003; Quigley 2007; Talayero 2006; Victora 2016; Wilson 1998). Non-exclusive breastfeeding may result in an earlier return of the mother's fertility and a shorter inter-birth interval (WHO 1999).

International actions work to improve the health of children and their mothers through the promotion of exclusive breastfeeding. The Baby Friendly Hospital Initiative (BFHI) is a global programme started in 1989 to protect and support exclusive breastfeeding through improvement of healthcare practices that affect infant feeding. It has an assessment criterion of 'Give newborn infants no food or drink other than breast milk unless medically indicated' (UNICEF/WHO 2009). In 2002, the World Health Assembly, supported by many national and international health associations, reiterated the importance of exclusive breastfeeding in the Global Strategy for Infant and Young Child Feeding. Their previous recommendation for exclusive breastfeeding for "four to six months" was amended to state that as a global public health recommendation, infants should be exclusively breastfeeding for the first six months of life and thereafter breastfeeding continued up to two years of age or beyond with the addition of adequate and safe complementary foods (WHO 2003).

From the data in the World Health Organization (WHO) Global Data Bank on Infant and Young Child Feeding 2009, it is estimated that only 38% of infants are exclusively breastfeeding for the first six months. There are indications that in many countries exclusive breastfeeding, though still low, has increased in the last decade (WHO 2014).

Supplementary feedings are classified as feeds provided in place of breastfeeding. These may include artificial baby milk, glucose water, teas, water or complementary semi-solid or solid) foods. Thus, any foods or fluids given before six months, the recommended duration of exclusive breastfeeding, are therefore defined as supplementary (AAP 2012; ABM 2009).

Studies on early additional fluids or foods tend to involve either additional fluids in the early weeks or the addition of foods at four to six months of age. Numerous health services, personal, socioeconomic and cultural factors influence the decision to supplement human milk. These factors include:

1. pre-lacteal feeds may be given in the belief that colostrum is harmful, or to clean the infant's gut (Davies-Adetugbo 1997);
2. early additional fluids are more likely following caesarean section (Ladomenou 2007), if hospital practices separate mother and infant at birth (Gagnon 2005; Kurinij 1991), or if the hospital does not follow practices in accordance with the WHO/UNICEF Baby Friendly Hospital Initiative (AAP 2012; Biro 2011);
3. additional fluids or foods may be given in the belief they will reduce maternal fatigue, by health workers (Cloherty 2004; Gagnon 2005), and by family members (Cohen 1999);
4. lack of health worker time to assist breastfeeding (Furber 2006; Gagnon 2005);
5. additional fluids or foods as the solution to the perception that the baby is unsettled due to low milk supply (Akuse 2002; Blomquist 1994; Gagnon 2005; Graffy 1992; Nicoll 1982), or to make the baby sleep longer;
6. maternal unrealistic expectations of newborn behaviour, difficulty in caring for a newborn, or other maternal concerns, and fluids other than mother's milk is seen as the solution to difficulties (DaMota 2012; Wagner 2013);
7. weight charts that are based on formula-fed infants or cultural beliefs about infant growth may imply that breastfeeding infants are underweight and additional fluids or foods are given in the belief they will result in higher weight gain that is thought to be beneficial (Sachs 2006; Vail 2015);
8. additional fluids are given in a belief that they will prevent dehydration, hypoglycaemia and neonatal jaundice (Akuse 2002; Nicoll 1982; Stewart 2015);
9. early introduction of allergenic foods in the belief this may reduce the incidence of later food allergy (Perkin 2016);
10. early maternal return to employment and lack of facilities in the workplace to breastfeed (Gielen 1991; Ladomenou 2007), and mothers perceive disapproval from society of breastfeeding outside her home (Bai 2009);
11. marketing of formula that suggests mother's milk is insufficient (Chezem 1998; Yee 2007);
12. translation of research into practice, even with the provision

of information and development of professional guidelines (ABM 2011), is sometimes met with barriers and delays (Brodribb 2008; Brodribb 2011).

Additional foods or fluids may be needed for medical reasons in specific situations related to the infant or mother. This review deals with the healthy, term infant and does not address individual needs or treatment in medical conditions. This review does not examine the use of oral sucrose solution for pain management in infants, oral probiotics, or interventions that provide promotion, education or support for increasing exclusive breastfeeding prevalence or duration.

How the intervention might work

Effects of early additional foods or fluids

It is difficult to obtain robust evidence about the effect of early additional foods and fluids (supplementation) on full-term, healthy, babies due in part to problems in the consistency of breastfeeding definitions (Labbok 2012), and of normal early neonatal weight change (Thulier 2016), poor research design (McNiel 2010; Renfrew 2007), publication bias (Boyle 2016), changes in composition of artificial milks over time,and the belief that supplementation is a routine acceptable practice, not an intervention, and thus does not need to be noted (Martin-Calama 1997; Mulford 1995). Early additional foods and fluids or exclusive breastfeeding may potentially affect the duration of breastfeeding, the infant immune system, infant morbidity and mortality, maternal infant bonding, as well as infant growth and development, length of postnatal hospital stay, physiological jaundice, maternal self-confidence and confidence in breastfeeding of those who influence the mother. Healthcare economics, family poverty, environmental burden and human development potential are also affected by the value put on exclusive breastfeeding (Rollins 2016).

Effect on duration of breastfeeding

Observational studies and surveys have found associations between early additional foods and fluids and shorter duration of breastfeeding (Blomquist 1994; Chantry 2014; Giovannini 2005; Hornell 2001; Kurinij 1991). The effect of early additional foods and fluids on reducing breastfeeding duration may include decreased milk production due to reduced removal of milk from the breast; difficulties in developing effective breastfeeding skills when the newborn infant is also feeding from a bottle and artificial teat which may result in low infant weight gain; or maternal sore nipples and breasts; all of which may result in early cessation of breastfeeding, as well as reduced maternal confidence in the ability to successfully breastfeed and the reinforcement of a negative belief that human milk is insufficient for an infant. Qualitative studies in the UK (Cloherty 2004; Furber 2006) have indicated that, despite their awareness of policies supporting exclusive breastfeeding, some midwives think that providing an occasional formula supplement in hospital may give the mother an opportunity to rest and be more likely to continue to breastfeed, thus an aid to longer duration.

Effect on infant morbidity and mortality

As mentioned earlier, infant mortality and morbidity may be affected by the addition of other fluids or foods to the infant in the first six months. The effect of early additional foods and fluids on infant morbidity and mortality may be related to a single factor or a combination of factors, including incorrectly prepared early additional foods and fluids, contamination of the fluid or food or the device used to give it (Horman 2010; Renfrew 2008; WHO 2007); receiving a reduced amount of the anti-infective nutrients in human milk (Ballard 2013); the effect of the non-human milk on the infant's developing immune and digestive systems; or other reasons (Turin 2014). Longer-term indications of morbidity related to immune reactions may include eczema and other skin conditions, asthma and digestive-related conditions (Horta 2013a; Ip 2007). Short-term indications of possible morbidity include hypo- or hyperthermia, hypo- or hyperglycaemia, diarrhoea, respiratory symptoms and otitis media (Horta 2013b; Kramer 2012; Victora 2016). An increased or reduced temperature may indicate an infection or other immune reaction. Normal temperature range is considered 36 to 38 degrees Celsius (97 to 100.4 degrees Fahrenheit). The advent of cot-side testing of blood glucose in the early 1970s led to attempts to define a level of asymptomatic hypoglycaemia that could be classified as a risk level, in the belief that treating at this level would reduce the risk of symptomatic hypoglycaemia occurring (Williams/WHO 1997). These older studies and textbooks were likely to use formula-fed infants as the norm and consider the values found in healthy breastfeeding infants as low. Transient hypoglycaemia is now understood as a normal adaptive response to the establishment of ex-utero feeding (ABM 2014), though extended hypoglycaemia may be an indication of illness. There is no agreed definition of hypoglycaemia as the value varies with the infant's maturity, pathology, clinical signs and method of testing. A suggested range of values considered as hypoglycaemia are between 30 and 50 mg/dL (1.7 to 2.8 mmol/L) (Wright 2006); however, older studies may use different values. Feeding healthy infants cow's milk formula in an attempt to raise their blood glucose levels to an unphysiological high level introduces non-human milk proteins, which may result in immunological reactions, possible bacterial contaminants and reduce the appetite of the infant to feed at the breast. Glucose water has additional risks from providing fewer calories than a similar volume of milk, thus filling the infant's stomach while providing insufficient nutrients. This increases the risks of hypoglycaemia and poor weight gain. There is no evidence that high blood glucose levels are of benefit to the infant, and high levels may affect the metabolic response, with later

effects on risks of obesity and diabetes. Diarrhoea may indicate an infection or an intolerance to foreign proteins or carbohydrates in non-milk feeds. As normal stools of a breastfeeding infant are much looser than the stools of a cow's milk formula-fed infant this makes the definition of diarrhoea open to interpretation. Breastfeeding provides for optimal immune system functioning and thus the level of respiratory infections and otitis media occurrences can indicate if there is an effect on the immune system.

Effect on physiological jaundice

Babies are born with fetal red blood cells which are no longer needed and must be metabolised and excreted. Bilirubin is a product of this breakdown, released in the blood stream and ultimately excreted in the baby's stool. A newborn's serum bilirubin level normally rises from birth until the third or fourth day postpartum and a significant proportion will have total serum bilirubin concentrations greater than 5.0 mg/dL (86 umol/L) while remaining healthy. This is termed physiological jaundice (ABM 2009). Ineffective feeding and thus reduced calorie intake can increase bilirubin levels (De Carvalho 1981; Yamauchi 1990). The normal initial fluid loss in newborn infants and situations of ineffective feeding leading to dehydration may lead to a belief that fluid supplements will prevent dehydration and jaundice, though the replacement of milk with water will further reduce the infant's calorie intake and has not been shown to reduce bilirubin levels (De Carvalho 1981; Houston 1984; Nicoll 1982). The replacement of breastfeeding with formula has been tested as a treatment to reduce high levels of serum bilirubin (Amato 1985; Osborn 1985), which may have led some health workers to use supplements to prevent high levels of bilirubin occurring (Akuse 2002).

Effect on infant growth and development

Weight loss in the newborn represents mainly fluid loss but may also involve loss of fat stores during the establishment of feeding (Wright 2004). A breastfeeding baby will commonly lose up to 5% to 7% in the first few days with no adverse effects (Thulier 2016). There may be a fear that the baby will become dehydrated until breastfeeding is established, and such babies are supplemented with water, glucose or artificial milk. Water, and glucose in particular, have no or little calorific value and may cause a baby to be full but remain deficient in calorific intake. Supplementation in such instances, as well as interfering with breastfeeding, will in fact contribute to further weight loss in the early postpartum period (Glover 1990). Evidence from studies in tropical climates demonstrate that breastfeeding babies will not become dehydrated if allowed to fully breastfeed on demand (Almroth 1990).

The WHO published comprehensive infant growth charts developed from data on breastfeeding infants (De Onis 2004). This long-term multi-centre study indicated that previous charts were likely to have categorised healthy breastfeeding infants as underweight, which may have contributed to the addition of foods and fluids before six months of age. Additional foods and fluids above the nutritional needs of the infant may result in the infant becoming overweight. Early introduction of complementary foods to breastfeeding infants is likely to result in less breast milk consumed, which may affect nutritional and immune status (Heinig 1993).

Confidence in breastfeeding

Antenatal or early postnatal breastfeeding self-efficacy of the mother is associated with more exclusive breastfeeding and longer duration of breastfeeding (Blyth 2004; Noel-Weiss 2006). If the mother or family members, health workers or others with influence on the mother have low confidence in the ability to breastfeed or the adequacy of mother's milk, this may lead to artificial formula supplementation and maternal feelings of failure (Hoddinott 1999; Wagner 2013). For the older infant, the decision to add formula or complementary foods may affect the duration of breastfeeding. Hornell suggests that formula given by bottle, because the mother perceived that she did not have sufficient milk, may reduce the duration of breastfeeding more so than complementary foods that are added because the mother thought the infant had reached an appropriate age (Hornell 2001).

Why it is important to do this review

Despite many years of widespread recommendations to support exclusive breastfeeding for four and more recently six months, common practice does not appear to reflect these recommendations suggesting there are perceived benefits from early additional fluids or foods. Given the potential risks from additional fluids or foods, this review aims to summarise the existing evidence on the effects of early additional food and fluids for breastfeeding full-term infants.

OBJECTIVES

The main objective of the review was to assess the benefits and harms of additional foods and fluids for full-term healthy breastfeeding infants. We also aimed to determine what impact the timing (during early phase of initiation of breastfeeding versus later on for maintenance) and type (water, artificial milk, foods) of additional foods and fluids had on these infants.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials (RCTs).

Types of participants

Full-term (that is 37 to 42 completed weeks' gestation (singleton or multiple births)) breastfeeding infants up to the age of six months (the currently recommended age after which complementary foods should commence), or the mothers of these infants.

Types of interventions

Breastfeeding with any additional food or fluids (once or more) in the first six months versus exclusive breastfeeding (as defined in the trial).

Types of outcome measures

Primary outcomes

1. Duration of breastfeeding
2. Incidence of infant morbidity, for example, hypo- or hyperthermia, hypo- or hyperglycaemia, gastro-intestinal infection, ear infection, asthma, eczema or other allergy (depending on how defined in individual trials)
3. Infant mortality (at discharge, 28 days, or one year)
4. Physiological jaundice, absence or presence, and if present, duration (days) (as defined in the Background)

Secondary outcomes

1. Measures of weight, growth and development (as defined by trial authors)
2. Duration of hospital stay (days)
3. Confidence in breastfeeding, for example of mothers, fathers, health workers or others with significant influence on the feeding of the infant (however assessed in individual trials)
4. Maximum serum bilirubin levels
5. Phototherapy in hospital or home setting if required, absence or presence, and if present, duration (days)

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist (1 March 2016).

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in the *Cochrane Library* and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Ongoing studies).

Searching other resources

We examined reference lists of all relevant retrieved papers to identify further studies.

We did not apply any language, geographic or date restrictions. For non-English articles, we reviewed the abstract and if RCT and the intervention or outcome was mentioned in the abstract we arranged further translation.

Data collection and analysis

For methods used in the previous versions of this review, *see* Becker 2011 and Becker 2014.

For this update, the following methods were used for assessing the reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Both review authors independently applied the inclusion criteria to all potential trials. We performed this without blinding. Two trials were discussed with a member of the Cochrane Pregnancy and Childbirth Group editorial office to assist in reaching agreement.

Data extraction and management

Both review authors independently extracted the data (using a customised data extraction form) and assessed the risk of bias of the selected trials. We resolved any disagreements through discussion. Both authors entered data into Review Manager software (RevMan 2014).

Assessment of risk of bias in included studies

Both review authors assessed each trial using a simple form and followed the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We also reported on whether the investigators had performed a sample-size calculation.
We compared assessments and resolved any inconsistencies by discussion.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

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

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

Given the nature of the interventions, blinding was generally not possible for participants and caregivers and so this was graded as an unclear risk of bias in this review.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and 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 could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.
We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

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

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update, the quality of the evidence was assessed using the GRADE approach as outlined in the GRADE handbook. We produced separate GRADE 'Summary of findings' tables summarising evidence for our three comparisons of: 1. non-exclusive breastfeeding (with artificial milk) versus exclusive breastfeeding; 2. non-exclusive breastfeeding (with water or glucose water) versus exclusive breastfeeding; and 3. non-exclusive breastfeeding (with additional foods) versus exclusive breastfeeding. Due to few trials with limited outcome data for the primary and secondary outcomes specified in this review, our 'Summary of findings' tables report different outcomes for different comparisons. We have not downgraded any evidence for lack of blinding (performance bias) and assessed the quality of the body of evidence relating to the following outcomes listed below:

1. duration of breastfeeding (at different time points);
2. infant morbidity (including: allergy related, hypoglycaemia, fever);
3. weight change (at different time points);
4. confidence in breastfeeding (maternal or of those influencing the mother).

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes were produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio (RR) with 95% confidence intervals, where appropriate.

Continuous data

For continuous outcomes, we recorded either the mean relative change from baseline for each group or mean post-treatment or post-intervention values and standard deviation. When standard errors were reported we converted these to standard deviations (as with Nicoll 1982). We calculated a pooled estimate of treatment effect by calculating the mean difference (MD).

Unit of analysis issues

The protocol for this review does not include cross-over trials or cluster-randomised trials. For studies that had multi-intervention arms, we first assessed which groups were relevant to this review and the appropriate method of analysis. If groups were similar, e.g. water and glucose water, then we combined the groups. If we found that more than two comparison groups were applicable, then we entered data as a single pair-wise comparison into RevMan 2014. In instances in which there were more than two groups to be compared, we took measures to avoid double counting or inappropriate totaling.

Dealing with missing data

We planned to enter the data on the number of participants by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up in order to allow an intention-to-treat analysis. However, this was not always possible, as for example, within some included trials, mothers who ceased to comply during the trial were excluded from the analysis (these trial authors did not provide outcome data on the full allocated group).

Assessment of heterogeneity

In future updates, when a sufficient number of trials are included in a meta-analysis, we plan to assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in a meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and we judged the trials' populations and methods to be sufficiently similar. In future updates, if there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detect substantial statistical heterogeneity, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

Where multiple time points have been reported within the included trial reports we have clearly reported when measurements were taken by the primary investigators during the trial, what measurements were reported within the published paper and what data we are reporting in the review.

Subgroup analysis and investigation of heterogeneity

When more data are included in the review, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses.

In future updates of this review we plan to carry out the following subgroup analysis:

1. timing of supplementation: given at early phase of initiation of breastfeeding (neonatal period - up to and including the first four weeks of life) compared with later on; for maintenance (after neonatal period) - (relating to primary outcomes (1), (2) and (3);
2. type of supplementation: water/ formula/glucose/food compared with each other - (relating to primary outcomes (1), (2) and (3);
3. geographical location: trials conducted in disadvantaged populations versus trials in advantaged populations - (relating to primary outcomes (2) and (3)).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

When sufficient trials are included in the review, for primary outcomes only, we plan to perform a sensitivity analysis based on the risk of bias of the trials, including and excluding quasi-randomised trials.

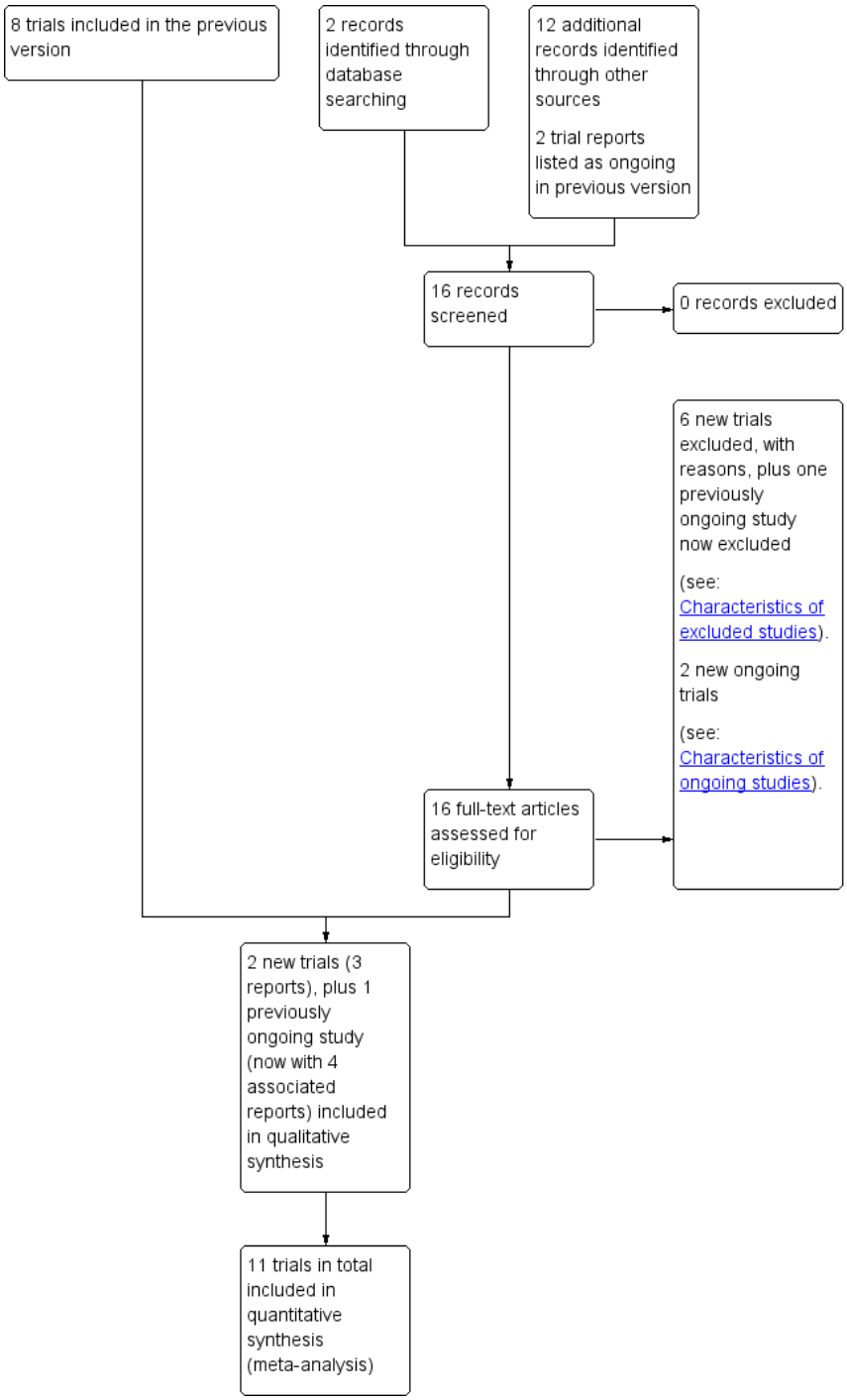
RESULTS

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.



An updated search in March 2016 retrieved 14 reports. We included two new trials (three reports) (Lindfors 1988; Straňák 2016). We also included another trial (four reports) previously listed as an ongoing study (Perkin 2016).
We identified two new ongoing trials (Flaherman 2014; Kair 2014).
We excluded six newly identified studies (Cameron 2015; de Jong 1998; Du Toit 2015; Juvonen 1996; Kimani-Murage 2013; Saarinen 1999), plus one previously ongoing study (Flaherman 2011).

Included studies

This review now includes 11 trials, in which a total of 2542 breastfeeding infants or their mothers were randomised (*see* Characteristics of included studies table). Four of the trials have multiple references; the Cohen trial has been reported in five individual papers, the Dewey trial in four, and the Jonsdottir in five plus a PhD thesis, Perkin (EAT trial) has published three papers at time of this review (Cohen 1994; Dewey 1999; Jonsdottir 2012; Perkin 2016), and two papers for Lindfors 1988. For each of the remaining six trials there is one paper published on each (Flaherman 2013; Martin-Calama 1997; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986; Straňák 2016).

Setting

Two trials were carried out in San Pedro Sula, Honduras (Cohen 1994; Dewey 1999) (these were associated trials); one in each of Teruel, Spain (Martin-Calama 1997); Ile-Ife, Nigeria (Ojofeitimi 1982); Philadelphia, USA (Schutzman 1986); London, UK (Nicoll 1982); San Francisco, USA (Flaherman 2013); Danderyd, Sweden (Lindfors 1988); Czech Republic (Straňák 2016); one across seven centres in Iceland (Jonsdottir 2012), and one trial including children across England and Wales (Perkin 2016).

Interventions

Seven trials were carried out in the first few days after birth and compared exclusive breastfeeding versus additional water and/or glucose water in four trials (Martin-Calama 1997; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986), and the addition of formula in three trials (Flaherman 2013; Lindfors 1988; Straňák 2016). One two-arm trial compared a 'glucose water' group (who received 5% glucose *ad libitum* from a bottle for the first three days of life in addition to breastfeeding), to a 'non-glucose water' group (who did not receive any alternative fluid to human milk) (Martin-Calama 1997). In a further two-arm trial, one group received glucose water feedings and the other colostrum (Ojofeitimi 1982). Another two-arm trial compared exclusive on-demand breastfeeding versus on-demand breastfeeding plus additional water where the choice of sterile water or 5% glucose water was left to the mother (Schutzman 1986). A three-arm trial compared an additional water group versus a non-supplement group versus a glucose supplement group (Nicoll 1982). One two-armed trial compared formula use before commencing breastfeeding with exclusive breastfeeding from birth (Lindfors 1988), and two similar trials compared exclusive breastfeeding versus breastfeeding plus a specific amount of formula added at specific intervals (Flaherman 2013; Straňák 2016).
Four trials compared continued exclusive breastfeeding to six months versus complementary feeding plus breastfeeding from three to six months (Cohen 1994; Dewey 1999; Jonsdottir 2012; Perkin 2016). One three-arm trial included an exclusive breastfeeding group versus a complementary foods group, with the introduction of complementary foods at 16 weeks, with *ad libitum* breastfeeding; or complementary foods and maintenance (SF-M), with the introduction of complementary foods at 16 weeks with maintenance of pre-intervention breastfeeding frequency (Cohen 1994). Two two-armed trials compared a group of continued exclusive breastfeeding to six months versus complementary feeding (plus breastfeeding from four to six months (Dewey 1999; Jonsdottir 2012). In the Dewey trial it was stated that mothers were encouraged to maintain baseline (16-week) breastfeeding frequency (Dewey 1999). The EAT Study (Enquiring About Tolerance) examined whether the early introduction of specific foods from three months of age plus continued breastfeeding in previously exclusively breastfeeding infants would prevent food allergies compared to levels in infants who were exclusively breastfeeding for approximately six months (Perkin 2016).

Outcomes

Outcomes (unless otherwise indicated) were to be measured at hospital discharge, three months and six months. We stated in the protocol that if outcome data were recorded at other time periods, we would consider examining these as well. Therefore, we have presented data for these other time periods that were reported.
Both of the included three-arm trials reported data for secondary outcomes 'weight change'; Nicoll also reported on 'maximum serum bilirubin levels' (Cohen 1994; Nicoll 1982). For each trial, we decided to combine the data for both of the supplemented interventions (water and glucose groups for the Nicoll trial; complementary foods and complementary foods with maintenance for the Cohen trial) into single intervention groups (supplemented group) to enable us to present these data within the analyses. In order to convert the sample sizes, means and standard deviations, we used the formulae as presented in the *Handbook* (Higgins 2011).
For the Martin-Calama trial and the outcome 'duration of breastfeeding' we estimated from the graph the percentage of mothers

breastfeeding at each time period (*see* Table 1), and calculated the number of women breastfeeding at each time period from these estimates, which enabled us to enter data on this outcome into the analysis.

The primary outcome 'incidence of morbidity' was considered to include trial outcomes related to any allergic symptoms including symptoms of food protein intolerances, as well as hypoglycaemia, fever, upper respiratory illness, anaemia. The secondary outcome of 'weight change' was broadened in this update to include measures of weight, growth and development, and 'maternal confidence' was broadened to include confidence in breastfeeding of mothers, fathers, health workers or others with significant influence on the feeding of the infant.

The nine included trials which provided data for analysis (n = 2226) reported on one (Flaherman 2013; Lindfors 1988) or two of the four primary outcomes (Cohen 1994; Dewey 1999; Martin-Calama 1997; Perkin 2016; Straňák 2016), and/or one (Flaherman 2013; Jonsdottir 2012) or two of the five secondary outcomes (Cohen 1994; Dewey 1999; Martin-Calama 1997; Nicoll 1982).

Two of the included trials did not report any data that were eligible for inclusion in the review (Ojofeitimi 1982; Schutzman 1986). In the Ojofeitimi trial, bacterial counts in fluids (colostrum and glucose water) and stools were reported, but no actual data on morbidity were reported (Ojofeitimi 1982). The outcome in the Schutzman trial was "arrival of true milk" (Schutzman 1986). As it is over 20 years since these two studies were published, we concluded that it was not feasible to seek further data from the trial authors.

Excluded studies

We excluded 30 trials from the review (see the Characteristics of excluded studies table). We excluded 18 because, on closer inspection, we identified that there was no exclusively breastfeeding group (Bannert 1995; Corchia 1985; Cronenwett 1992; de Jong 1998; Du Toit 2015; French 2012; Gray-Donald 1985; Juvonen 1996; Kearney 1990; Ly 2006; Rosegger 1985; Rosegger 1986; Sachdev 1991; Schiess 2010; Schmitz 1992; Schubiger 1997; Simondon 1996; Ziegler 2011). We excluded four trials that included only preterm infants (Collins 2004; Howard 2003; Marinelli 2001; Mosley 2001), two trials that compared regimens of the iron-containing foods used (Krebs 2013; Olaya 2013), and one trial protocol that was to examine treatment of a condition (Flaherman 2011). We assessed two trials, which on closer inspection, we considered as not being randomised or quasi-randomised (De Carvalho 1981; Saarinen 1999). Three trials related to effects of counselling in preventing the introduction of other foods or fluids before six months (de Oliveira 2012: Cameron 2015; Kimani-Murage 2013).

Risk of bias in included studies

We assessed each trial for risk of bias as outlined in the Methods section. We have presented summary descriptions of the assessments on the risk of bias in Figure 2 and Figure 3, and provided details of the assessment for each trial in Characteristics of included studies.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

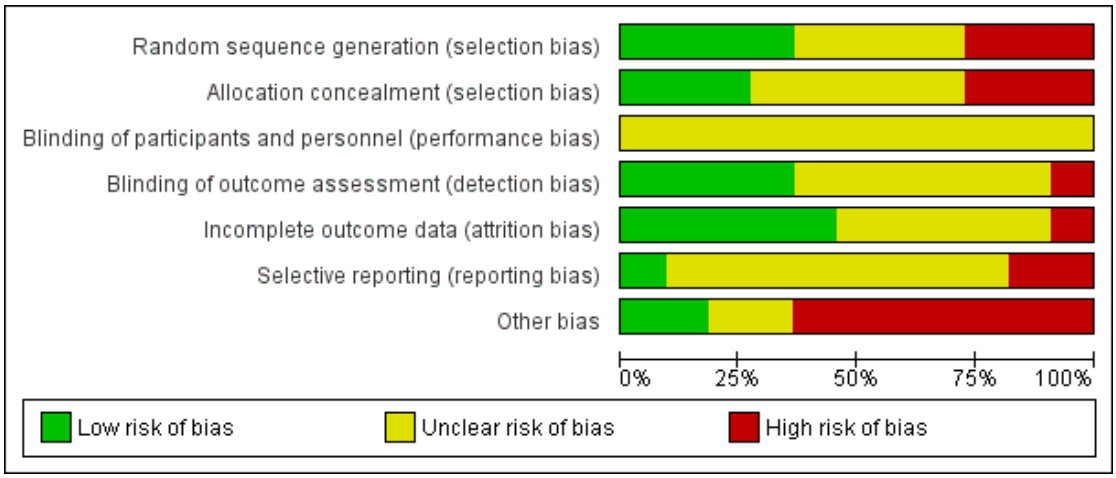
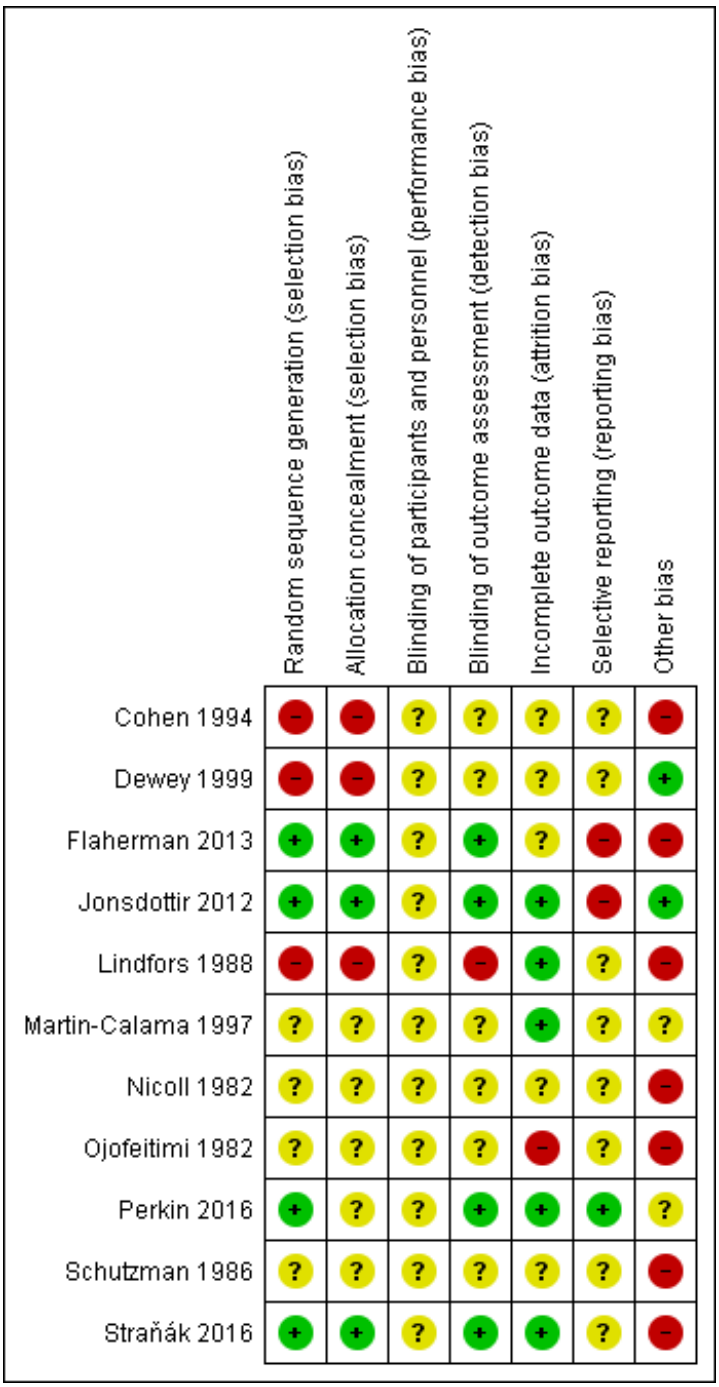


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We assessed sequence generation and concealment of allocation as low risk in three trials (Flaherman 2013; Jonsdottir 2012; Straň ák 2016); high risk in three trials (Cohen 1994; Dewey 1999; Lindfors 1988); and of unclear risk in four trials (Martin-Calama 1997; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986). Perkin 2016 was assessed as low risk for sequence generation and unclear risk for concealment of allocation.

Blinding

Given the nature of the interventions blinding was not possible for participants and caregivers. As a result we graded all studies as having an unclear risk for performance bias. There was no information provided by six of the included trials with regards to whether outcome assessors were blinded or not (Cohen 1994; Dewey 1999; Martin-Calama 1997; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986). Therefore, we assessed these six trials as having an unclear risk of detection bias. For the Jonsdottir trial, while nurses who collected data on complementary food intakes and anthropometric outcomes were not blinded to participant group status, those who undertook all mass spectrometric analyses and isotopic modelling were blinded, therefore we considered this study as having a low risk of detection bias (Jonsdottir 2012). A blinded research assistant assessed outcome data for the Straň ák and Flaherman trials, which we assessed as having a low risk (Flaherman 2013; Straň ák 2016). Perkin 2016 replied to our query that the outcome assessors were not blinded however that outcome was based on strict set objectivity measures of allergic sensitivity, thus this was rated at low risk of detection bias.

Lindfors 1988 reported that all paediatricians who assessed for allergy symptoms when infants were 18 months old "were unaware of the feeding regimen" however they "scrutinized the history, and then filled in a detailed form concerning feeding" and this may have resulted in the group allocation being disclosed; therefore the study was graded as high risk.

Incomplete outcome data

Five studies clearly documented reasons for any incomplete outcome data and therefore, we assessed these as having a low risk of bias for this domain (Jonsdottir 2012; Lindfors 1988; Martin-Calama 1997; Perkin 2016; Straň ák 2016). Three of these trials ((Jonsdottir 2012; Martin-Calama 1997; Straň ák 2016) reported similar dropout rates between treatment groups. Lindfors reported numbers lost to follow-up at each stage with low loss over five years and similar loss in both groups.

We assessed five trials as having an unclear risk of bias (Cohen 1994; Dewey 1999; Flaherman 2013; Nicoll 1982; Schutzman 1986). The published data from the Cohen and Dewey trials report analyses based on compliance with allocation, not intention-to-treat (Cohen 1994; Dewey 1999). For the Cohen trial, the dropout rate differed significantly between treatment groups, for the randomised controlled part of the Dewey trial, dropout rates between treatment groups were not balanced and there were significant differences in some patient characteristics, for this domain we therefore assessed these two trials as having an unclear risk of bias. A further trial reported that a high percentage of mother/baby pairs defaulted and were replaced by further randomised pairs in one of the three arms of the trial, we therefore also assessed this as having an unclear risk of bias (Nicoll 1982). No reference to dropouts was reported in Schutzman 1986, while in Flaherman 2013 information on missing data was not clearly reported.

In the Ojofeitimi trial, participation was voluntary, and those mothers who failed to adhere were excluded from the trial (42%); we therefore assessed this trial as having a high risk of bias for this domain (Ojofeitimi 1982).

Selective reporting

Seven studies reported data on all the outcomes mentioned in the 'Methods' section of their articles (Cohen 1994; Dewey 1999; Lindfors 1988; Martin-Calama 1997; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986), though not at all the time periods were mentioned. We did not retrieve any of the protocols or raw data of these trials and thus did not identify whether outcomes other than those reported within the papers were collected but not reported on. We have therefore assessed this domain as having an unclear risk of bias for these trials.

One study (Straň ák 2016) measured and recorded clinical outcomes that were not pre-determined as study outcomes in the registered protocol and we marked this study as having an unclear risk of bias.

The Flaherman and Jonsdottir trials were registered trials with protocols available (Flaherman 2013; Jonsdottir 2012). The protocol for the Flaherman trial referred to outcomes of weight nadir and maternal satisfaction, which are not referred to in the published trial report, and the introduction to the report refers to effect on infant weight, however only loss is reported, not any weight gain. The protocol for the Jonsdottir trial referred to secondary outcomes of upper respiratory infections and diarrhoeal episodes, although in one of the published references to this study (Wells 2012) it states "Finally, our study was designed to evaluate growth and energy intake and not other issues such as development of dietary preferences, mineral status, or effects on health such as diarrhoea and allergy". We therefore assessed these two trials as having a high risk of bias for this domain. For Perkin 2016 there was a protocol published, very extensive appendices on-line with

additional data and additional publications are planned to report further on outcomes, thus we assessed this study as low risk of reporting bias.

Other potential sources of bias

Two studies (Dewey 1999; Jonsdottir 2012) were assessed as being low risk for other sources of potential biases. Two studies were graded as having a unclear risk. In one trial, telephone follow-up at five months was used to collect data on the exclusiveness and duration of breastfeeding during the previous 20 weeks, which could be a possible source of recall bias and lack of consensus to what is considered a risk level of low serum glucose in the first few days after birth (Martin-Calama 1997); there was low adherence to the study protocol in the intervention group in the other study (Perkin 2016).

The remaining seven studies were all graded as high risk for other sources of potential biases. Flaherman 2013 and Straň ák 2016 were graded as high risk due to their inclusion criteria of weight loss of ≥ 5% in the first few days after birth, though this is well within the range of normality. This may have influenced those involved to consider there was a problem with exclusive breastfeeding when there was not and result in overuse of formula supplementation. The publications from both studies reported no direction given as to how often to give the supplement beyond "after each breastfeed". Further communication with the Straň ák team provided the information that the supplement was given on a three-hourly schedule; feeding to a schedule could conflict with the protocol of feeding in response to baby signs (demand feeding) and this might limit the number of breastfeeds. With both studies, the supplement was given by oral syringe and the infant was not able to refuse the supplement if already content with the amount of breast milk consumed. Additional information also clarified that definitions used for exclusive breastfeeding at a time point related to the previous 24 hours only and thus giving a different result than if the definition used was the time since birth as per WHO definitions. In Flaherman 2013 at the start of the intervention, of those replying (15% did not reply), 47% of the formula supplementation group and 32% of the exclusive breastfeeding group had previously planned to use infant formula in addition to breastfeeding, which may have affected their motivation to comply with the allocation. Compliance with allocation is not reported. Other variables known to effect exclusive breastfeeding and weight change, such as birth practices, information and support, feeding in response to infant cues ("demand feeding") and skilled assistance, were not included. Though the effect on weight is an outcome of the Flaherman trial, the trial did not include a weighing protocol and relied on weights routinely collected, which varied as to what time points these were collected (additional information from trialist). Lindfors 1988 referred to infants being breastfeed "when the mother's breast milk production started" with no information if this meant colostrum or Lactogenesis II and if the infants in the breastfeeding group might have received water/glucose water if mother's milk was not expected to be present for a few days. There was a high number of outcome assessors working independently and diagnosis of allergy was based on clinical criteria with no laboratory testing at 18 months. For these reasons Lindfors 1988 was graded as high risk for other bias.

Most older studies (Cohen 1994; Lindfors 1988; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986) did not demonstrate any evidence of undertaking a power calculation to determine their sample size and were rated as high risk for bias. Flaherman 2013 states: "The sample size was chosen as a pilot to demonstrate feasibility".

Effects of interventions

See: **Summary of findings for the main comparison** Non-exclusive breastfeeding (artificial milk) versus exclusive breastfeeding; **Summary of findings 2** Non-exclusive breastfeeding (water or glucose water) versus exclusive breastfeeding; **Summary of findings 3** Non-exclusive breastfeeding (foods) versus exclusive breastfeeding

We included 11 trials (n = 2542 randomised infants or their mothers). The variation in use of outcome measures and time points in different trials made it difficult to pool results from trials. Nine trials (n = 2226) provided data on outcomes of interest to this review. Data could only be combined in a meta-analysis for one primary outcome (breastfeeding duration) (Flaherman 2013; Straň ák 2016) and one secondary outcome (weight change) for two studies (Cohen 1994; Dewey 1999). None of the included studies reported on physiological jaundice, absence or presence, and if present, duration (days) (as defined in the Background). Only one trial reported on infant mortality (Perkin 2016). The trials that provided outcome data compared exclusively breastfeeding infants with breastfeeding infants who were provided with additional artificial milk (Flaherman 2013; Lindfors 1988; Straň ák 2016), glucose water/water (Martin-Calama 1997; Nicoll 1982) or complementary foods (Cohen 1994; Dewey 1999; Jonsdottir 2012; Perkin 2016).

See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3 for the quality of evidence for each of the three main comparisons.

Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infant (comparison 1)

Primary outcomes

1. Duration of breastfeeding

This outcome was reported in two trials (139 pairs analysed) (Flaherman 2013; Straň ák 2016).The Flaherman and Straň ák

trials used a similar protocol to compare non-exclusively breastfeeding infants who were provided with artificial milk in the first few days after birth with exclusively breastfeeding infants. The intervention of additional artificial milk did not effect the number of infants with any breastfeeding at hospital discharge (risk ratio (RR) 1.02, 95% confidence interval (CI) 0.97 to 1.08; participants = 100; *low-quality evidence*) and the intervention resulted in a marginally higher number with exclusive breastfeeding in the 24 hours prior to discharge (RR 1.11, 95% CI 1.00 to 1.24; participants = 100) Straňák 2016. The results from a similar intervention by Flaherman 2013 indicated the additional artificial milk intervention resulted in a marginally higher number with exclusive breastfeeding in the 24 hours prior to data collection at one week (RR 1.71, 95% CI 1.09 to 2.68; participants = 39). Both trials (Flaherman 2013; Straňák 2016) measured the method of feeding at three months which combined results indicated the group fed additional artificial milk in hospital were more likely to be exclusive breastfeeding in the previous 24 hours (RR 1.43, 95% CI 1.15 to 1.77; participants = 138), and more likely at three months to have any breastfeeding in the previous 24 hours (RR 1.21, 95% CI 1.05 to 1.41; participants = 137; *low-quality evidence*) (Analysis 1.1).

Adherence to protocol was low among the exclusive breastfeeding group. Flaherman 2013 reported that during the first week after birth, newborn infants assigned to additional artificial milk intervention received 116 ± 110 mL artificial milk, and controls (exclusive breastfeeding) received 262 ± 411 mL; intervention period began at 24 to 48 hours until 72 to 106 hours of age. Straňák 2016 reported that "Only 11 out of 50 (22%) infants in the control group were exclusively breastfeeding during hospitalisation"; the total control group (exclusively breastfeeding) received 475 mL of artificial milk feeds and the study group received 400 mL of artificial milk additional feeds.

2. Incidence of infant morbidity

Flaherman 2013 and Lindfors 1988 examined the effect of non-exclusive breastfeeding with artificial milk to exclusive breastfeeding in the first few days after birth on the incidence of fever (Analysis 1.3) and allergy symptoms (Analysis 1.2), respectively.

The use of additional artificial milk had no effect on the incidence of fever (RR 1.06, 95% CI 0.83 to 1.36; participants = 28), but did show a protective effect against "obvious or probable symptoms" of allergy at 18 months of age (RR 0.56, 95% 0.35 to 0.91; participants = 207; *very low-quality evidence*) compared to exclusive breastfeeding. It should be noted that the trialists reported that no diagnostic challenges or other tests were performed to confirm the allergy symptoms (Lindfors 1988).

Secondary outcomes

1. Confidence in breastfeeding

The intervention of supplementation with artificial milk in the first few days after birth showed no difference in maternal confidence measured by a modified breastfeeding self-efficacy score at week one (mean difference (MD) 0.10, 95% CI -0.34 to 0.54; participants = 39; *low-quality evidence*) (Flaherman 2013) (Analysis 1.4). The modified breastfeeding self-efficacy score consists of Items rated on a scale from 1 ("Strongly Disagree") to 5 ("Strongly Agree"), with higher scores associated with increased breastfeeding self-efficacy.

2. Phototherapy in hospital or home setting if required, absence or presence, and if present, duration (days)

The intervention of additional artificial milk in the first few days after birth did not show an effect on the incidence of requiring phototherapy; one incidence of phototherapy in the control group was reported as lasting 48 hours and none reported in the intervention group (RR 0.33, 95% CI 0.01 to 7.99; participants = 100) (Straňák 2016) (Analysis 1.5).

The following secondary outcomes were not reported in the trials: measures of weight, growth and development, duration of hospital stay and maximum serum bilirubin levels.

Non-exclusive breastfeeding (water or glucose water) versus exclusive breastfeeding infants (comparison 2)

Primary outcomes

1. Duration of breastfeeding

Martin-Calama 1997 (n = 170) compared breastfeeding infants who were provided with additional glucose water versus exclusively breastfeeding infants. Breastfeeding duration was evaluated at four, eight, 12, 16 and 20 weeks (and presented as a graph). We have estimated from the graph the percentage of mothers breastfeeding at each time period (see Table 1) and calculated the number breastfeeding at each time period from these estimates. The additional glucose water did not improve the number of infants breastfeeding. The likelihood of infants continuing to breastfeed was lower in the non-exclusive breastfeeding (additional glucose water) group across all five time periods (participants = 170): at four weeks (RR 0.83, 95% CI 0.73 to 0.94); at eight weeks (RR 0.79, 95% CI 0.65 to 0.96); at 12 weeks (RR 0.68, 95% CI 0.53 to 0.87; *low-quality evidence*); at 16 weeks (RR 0.65, 95% CI 0.49 to 0.87); and at 20 weeks (RR 0.69, 95% CI 0.50 to 0.95) (Analysis 2.1). We do note that the trial authors report that this difference had disappeared at the end of 20 weeks, which is not the case in our analysis.

2. Incidence of infant morbidity

Hypothermia or hyperthermia

The addition of glucose water to breastfeeding babies did not show any clinically significant difference in infants' mean maximum temperature and mean minimum rectal temperatures measured at 72 hours of age by Martin-Calama 1997 (170 infants analysed); mean difference in the maximum temperature (degrees Celcius) (MD -0.10, 95% CI -0.19 to -0.01) and minimum temperature (MD -0.10, 95% CI -0.18 to -0.02), respectively (Analysis 2.2; Analysis 2.3). The trial author states that three infants (1%, all in the exclusively breastfeeding group) had a temperature exceeding 38 degrees C (the level generally accepted as fever) and does not report any occurrences of hypothermia of clinical concern.

Hypoglycaemia or hyperglycaemia

The addition of glucose water resulted in a lower number of episodes of hypoglycaemia in the glucose water group compared to the exclusive breastfeeding group. The difference was originally lower at 12 hours (RR 0.07, 95% CI 0.00 to 1.20; participants = 170; *very low-quality evidence*) with no significant difference reported at six hours (RR 0.42, 95% CI 0.08 to 2.10; participants = 170), at 24 hours (RR 1.57, 95% CI 0.27 to 9.17; participants = 170; *very low-quality evidence*), or at 48 hours (RR 0.35, 95% CI 0.04 to 3.29; participants = 170) Martin-Calama 1997 (Analysis 2.4). Trialists used a cut-off point as serum glucose less than 2.2 mmol/L and they point out that there is no consensus on the risk level and some researchers define a lower cut-off level (1.7 mmol/L). Overall, the number of episodes was low and trialists report there was no case of serum glucose levels under 1.7 mmol/L in either of the two groups and no cases presented hypoglycaemic symptoms.

The addition of glucose water to healthy full-term breastfeeding infants marginally increased the mean serum (capillary) glucose level (mmol/L) in the glucose water group compared to the exclusive breastfeeding group, measured at six hours after birth (MD 0.29, 95% CI 0.02 to 0.56; participants = 170), 12 hours (MD 0.47, 95% CI 0.24 to 0.70) and 24 hours (MD 0.34, 95% CI 0.08 to 0.60) though the difference was no longer evident at 48 hours (MD 0.24, 95% CI -0.03 to 0.51) Martin-Calama 1997 (Analysis 2.5).

Secondary outcomes

1. Measures of weight, growth and development

It is common for infants to lose some weight in the first 48 hours after birth as excess fluid is shed. The addition of glucose water to breastfeeding babies showed a reduced weight loss (grams (g)) in the intervention group compared to exclusively breastfeeding babies, measured at six hours (MD -7.00 g, 95% CI -13.24 to -0.76; participants = 170); 12 hours (MD -11.50 g, 95% CI -21.29 to -1.71; participants = 170); 24 hours (MD -13.40 g, 95% CI -26.37 to -0.43; participants = 170); and at 48 hours (MD -32.50 g, 95% CI -52.09 to -12.91; participants = 170; *low-quality evidence*), respectively. However, at 72 hours, there was no significant difference between the groups in infant weight loss (MD 3.00 g, 95% CI -20.83 to 26.83; participants = 170; *very low-quality evidence*) (Analysis 2.6). The trialists report that "weight loss did not exceed 7% in either group" (Martin-Calama 1997).

The percentage weight loss was reported on day three and five for each of the three groups. The authors state that the percentage weight loss on day three was significantly lower in the additional glucose water group compared to the exclusive breastfeeding group and the water supplemented group (presumed by trial authors to be due to marginally greater hydration), the authors also state that this difference was not apparent by day five. When we analysed the data from the glucose water and the water groups as one intervention arm, and compared this to the exclusive breastfeeding group, we found no significant difference in weight loss between the combined supplemented group and the exclusive breastfeeding group on either day three or day five (MD -1.03%, 95% CI -2.24 to 0.18; participants = 47; *very low-quality evidence*) and (MD -0.20%, 95% CI -0.86 to 0.46; *very low-quality evidence*), respectively (Nicoll 1982) (Analysis 2.7).

2. Maximum serum bilirubin levels

One three-arm trial (Nicoll 1982) compared additional water or additional glucose water with exclusive breastfeeding in the first few days after birth and we have presented data for the additional fluids groups combined. The mean plasma bilirubin levels on day six (µmol/L) was higher in the additional water and the glucose water groups combined compared to the exclusively breastfeeding group (MD 18.84, 95% CI -1.35 to 39.03; participants = 47) (Analysis 2.8). A table in the published trial report shows the plasma bilirubin levels across the three groups as mean (SE) additional water 93.5 µmol/L (13.8), glucose water 80.8(8.8), and exclusive breastfeeding 67.7(6.7), all well within the clinical low-risk zone that extends to 222 µmol/L at 144 hours (six days) (American Academy of Pediatrics).

The following secondary outcomes were not reported in the trials: duration of hospital stay, confidence in breastfeeding and phototherapy in hospital or home setting.

Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants (comparison 3)

Primary outcomes

1. Duration of breastfeeding

Among these older infants, Perkin 2016 (participants = 1162) reports in their published appendix that the median duration of any breastfeeding was similar in both groups, 50.2 weeks in the standard group (exclusive breastfeeding) and 49 weeks in the early introduction of potential allergenic foods intervention group.
Jonsdottir 2012 (participants = 100) retrospectively collected information on total duration of breastfeeding for all infants. However, we are unable to present these data as they were combined with data from an additional cohort of infants from a separate national prospective study.

2. Incidence of infant morbidity

Fever

The addition of complementary foods to infants at four months versus six months showed no evidence of difference in the reported prevalence (percentage of days) of fever in infants aged from 16 to 26 weeks (MD -0.70 day, 95% CI -3.40 to 2.00; participants = 119; *low-quality evidence*) (Dewey 1999) (Analysis 3.1).

Upper respiratory illness

The prevalence (percentage of days) of cough, congestion, nasal discharge and hoarseness in breastfeeding infants receiving additional foods from four months versus exclusive breastfeeding to six months was reported from 16 to 26 weeks (Dewey 1999). There was no difference between groups in the percentage of days with cough (MD 3.10, 95% CI -4.52 to 10.72; participants = 119) (Analysis 3.2); with congestion (MD 3.60, 95% CI -3.41 to 10.61; participants = 119) (Analysis 3.3); with nasal discharge (MD 4.20, 95% CI -1.13 to 9.53; participants = 119) (Analysis 3.4); with hoarseness (MD 0.10, 95% CI -1.84 to 2.04; participants = 119) (Analysis 3.5).
In one trial, Cohen (participants = 141) reported narratively (no data provided) that upper respiratory illness was relatively uncommon; the prevalence was approximately 4% of days between 16 and 26 weeks. The trial authors reported that the additional food group had a lower prevalence of respiratory illness than the exclusively breastfeeding group which reflected a difference in coughs. When fever accompanied a respiratory illness (less than 1% of days), there was no difference in prevalence among groups (Cohen 1994).

Diarrhoea

Breastfeeding infants receiving additional foods from four months versus exclusive breastfeeding to six months was reported from 16 to 26 weeks, participants = 119 (Dewey 1999). The trial authors used a nonparametric test for non-normally distributed data when analysing this outcome, therefore we have not entered it into the RevMan analysis. They report that the prevalence of diarrhoea (defined by the researchers as more than three liquid stools per day) was less common in the additional foods group (percentage of days, mean (SD), 2.8% (5.4%) versus 5.4% (8.5%) in the complementary food group). The report states: "The difference was marginally significant (1.4% +/- 3.0% in the additional foods group compared with 2.9% +/- 5.0% in the exclusive breastfeeding group) when diarrhoea was defined as more than five liquid stools per day. The difference in proportion of days with diarrhoea was due to a difference in the number of episodes (no data provided), not to the duration of episodes" (Dewey 1999).
Cohen (participants = 141 pairs) did not report any morbidity data but narratively reported that diarrhoea was relatively uncommon, with a prevalence of approximately 4% of days between 16 and 26 weeks and that morbidity from diarrhoeal disease was similar among groups (Cohen 1994).

Allergies

Early introduction of potentially allergenic foods was not found to reduce the risk of "food allergy" to one or more of these foods between one to three years of age compared to the group exclusively breastfeeding to about six months (RR 0.80, 95% CI 0.51 to 1.25; participants = 1162; *moderate-quality evidence*) (Analysis 3.6). Nor was the early introduction of these foods found to reduce the risk of visible eczema at 12 months stratified by visible eczema at enrolment (at three months of age) (RR 0.86, 95% CI 0.51 to 1.44; participants = 284; *moderate-quality evidence*) (Analysis 3.7). Food protein-induced enterocolitis syndrome reactions were reported by families for 10 children and on food challenge, three children were reported with positive reactions, one in the early allergen foods and two in the control group (RR 2.00, 95% CI 0.18 to 22.04; participants = 1303; *moderate-quality evidence*) (Analysis 3.8) (Perkin 2016) (Tables S6 and S9 in study appendix).

Anaemia

Jonsdottir measured iron deficiency anaemia (the criteria for iron-deficiency anaemia (IDA) required that all three indicators met the following cut-off points: haemoglobin (Hb), 105 g/L, mean cell volume (MCV), 74 fl, and complementary food (CF), 12 mg/L) (Jonsdottir 2012). Two infants had iron deficiency anaemia (one in the exclusive breastfeeding group, one in the early complementary foods group). No significant differences were reported between groups in iron deficiency with or without anaemia.

3. Infant mortality (at discharge, 28 days or one year)

One of the included studies reported on this outcome with no deaths occurring in either group (Perkin 2016).

Secondary outcomes

1. Measures of weight, growth and development

Breastfeeding infants receiving additional foods from four months showed no clinically meaningful difference in infant weight gain (g) from 16 to 26 weeks compared to exclusive breastfeeding to six months (MD -39.48 g, 95% CI -128.43 to 49.48; participants = 260; *low-quality evidence*) (Analysis 3.9) (Cohen 1994; Dewey 1999), or using infant weights calculated as z scores (World Health Organization), (MD -0.01 SD, 95% CI -0.15 to 0.13; participants = 100; *moderate-quality evidence*) (Jonsdottir 2012) (Analysis 3.10). Furthermore, Jonsdottir 2012 reported that the introduction of complementary foods at four months did not affect the prevalence of overweight children at 18 months (P = 0.74) or 29 to 38 months of age (P = 0.36).

2. Confidence in breastfeeding

As part of the larger study of mothers of low birthweight infants in Honduras (Dewey 1999), the mothers' reactions to attempting to breastfeed exclusively for four or six months and the obstacles they encountered were explored using interviews, focus groups and views of the field workers (Cohen 1999). The study authors narratively reported that at two weeks 87% of the mothers said that they were confident in their ability/desire to breastfeed exclusively, rising to 96% to 97% at eight to 12 weeks, with those who did not maintain exclusive breastfeeding being less confident. Confidence is not reported by the groups of exclusive breastfeeding to six months and additional foods from four months.

There may be a lack of confidence in exclusive breastfeeding for six months and later outcomes. A higher number of parents in the exclusive breastfeeding group expressed concerns about their child's development or behavioural status at 18 months (44% exclusive breastfeeding group versus 17% complementary foods group), though the difference was not significant when adjusted for baseline differences (P = 0.08); and at 30 to 35 months (19% exclusive breastfeeding group versus 2% complementary foods group), which remained significant after adjustment (P = 0.03), however no significant inter-group differences in the children's developmental measures were found (Jonsdottir 2012).

The following secondary outcomes were not reported in the trials: duration of hospital stay,maximum serum bilirubin levels and phototherapy in hospital or home setting.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Non-exclusive breastfeeding (water or glucose water) versus exclusive breastfeeding

Patient or population: healthy breastfeeding full-term infants
Setting: hospital setting in Spain and UK
Intervention: non-exclusive breastfeeding infants (water or glucose water)
Comparison: exclusive breastfeeding infants

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with exclusive breastfeeding infants	Risk with non-exclusive breastfeeding infants (water)				
Any breastfeeding at 12 weeks	Study population		RR 0.68 (0.53 to 0.87)	170 (1 RCT)	⊕⊕◯◯ LOW [1,2]	Estimated from the graph the percentage of mothers breastfeeding at each time period (see Table 1).
	747 per 1000	508 per 1000 (396 to 650)				
Hypoglycaemia episodes at 12 hours of life (glycaemia < 2.2 mmol/L)	Study population		RR 0.07 (0.00 to 1.20)	170 (1 RCT)	⊕◯◯◯ VERY LOW [1,3,4]	Trialists used a cut-off point as serum glucose less than 2.2 mmol/L whereas some researchers define a lower cut-off level (1.7 mmol/L). Trialists report there was no case of serum glucose levels under 1.7 mmol/L in either of the 2 groups and no cases presented hypoglycaemic symptoms

	80 per 1000	6 per 1000 (0 to 97)				
Hypoglycaemia episodes at 24 hours of life (glycaemia < 2.2 mmol/L)	Study population		RR 1.57 (0.27 to 9.17)	170 (1 RCT)	⊕◯◯◯ VERY LOW [1,3,4]	Trialists used a cut-off point as serum glucose less than 2.2 mmol/L whereas some researchers define a lower cut-off level (1.7 mmol/L). Trialists report there was no case of serum glucose levels under 1.7 mmol/L in either of the 2 groups and no cases presented hypoglycaemic symptoms
	23 per 1000	36 per 1000 (6 to 211)				
Weight change (loss) (g) at 48 hours	The mean weight loss (g) at 48 hours was 197.8 g (SD 73.2)	Infants with additional fluids (water) were on average (MD) 32.5 g heavier (less weight lost) (CI 12.91 g heavier to 52.09 g heavier)	-	170 (1 RCT)	⊕⊕◯◯ LOW [1,2]	This mean difference of 32.5 g is not clinically meaningful.
Weight change (loss) (g) at 72 hours	The mean weight loss (g) at 72 hours was 141.9 g (SD 89.1)	Infants with additional fluids (water) were on average (MD) 3 g lighter (more weight lost) (CI 26.83 g lighter to 20.83 heavier)	-	170 (1 RCT)	⊕◯◯◯ VERY LOW [1,3]	
Weight loss (%) day 3 (percentage of birthweight)	The mean weight loss (%) day 3 was 6% of birthweight	Infants with additional fluids (water) lost on average (MD) 1.03% less of their birthweight (CI 2.24% less to 0.18%	-	47 (1 RCT)	⊕◯◯◯ VERY LOW [1,3]	We combined the glucose and water supplement arms of the Nicoll 1982 trial.

		more weight lost)				
Weight loss (%) day 5 (percentage of birthweight)	The mean weight loss (%) day 5 was 4.3% of birthweight	Infants with additional fluids (water) lost on average (MD) 0.2% less of their birthweight (CI 0.86% less to 0.46% more weight lost)	-	47 (1 RCT)	⊕◯◯◯ VERY LOW [1,3]	We combined the glucose and water supplement arms of the Nicoll 1982 trial.
Confidence in breastfeeding (maternal or of those influencing the mother)						This outcome was not reported.

*__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; **MD:** mean difference; **RR:** Risk ratio

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

[1] 1 trial with no information on sequence generation or allocation concealment (-1).
[2] Evidence based on small sample size (-1).
[3] Wide confidence intervals crossing the line of no effect and small sample size (-2).
[4] Few events

Non-exclusive breastfeeding (foods) versus exclusive breastfeeding

Patient or population: healthy breastfeeding full-term infants
Setting: home setting in Honduras, Iceland and the UK
Intervention: non-exclusive breastfeeding infants (foods)
Comparison: exclusive breastfeeding infants

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Exclusive breastfeeding infants	Risk with non-exclusive breastfeeding infants (foods)				
Duration of breastfeeding (at different time points)						This outcome was not reported in a format that could be analysed
Fever (% of days) - 4 to 6 months	The mean fever (% of days) - 4 to 6 months was 8% days (SD 7.2)	Infants with additional foods had a fever on average 0.7% of days lower (CI 3.4% fewer to 2% more days)	-	119 (1 RCT)	⊕⊕◯◯ LOW [1,2]	
"Food allergy" to 1 or more foods between 1 to 3 years of age	Study population		RR 0.80 (0.51 to 1.25)	1162 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	There was low adherence to the protocol in the intervention group
	71 per 1000	56 per 1000 (36 to 88)				
Visible eczema at 12-month visit stratified by visible eczema at enrolment	Study population		RR 0.86 (0.51 to 1.44)	284 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	There was low adherence to the protocol in the intervention group
	182 per 1000	156 per 1000 (93 to 262)				

Food protein enterocolitis syndrome positive response to challenge (number of children)	Study population		RR 2.00 (0.18 to 22.04)	1303 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	There was low adherence to the protocol in the intervention group
	2 per 1000	3 per 1000 (0 to 34)				
Weight change (gain) (g) - 4 to 6 months	The mean weight change (gain) (g) at 4 to 6 months was 1054 g	Infants with additional foods gained on average (MD) 39.48 g less weight (CI 128.43 g less to 49.48 g more weight gain)	-	260 (2 RCTs)	⊕⊕◯◯ LOW [12]	
Weight change (z score) as standard deviations of an overall population distribution of infant weight gain at 4 - 6 months	The mean weight change (z score) was 0.01 standard deviations less weight gained	The mean weight change for infants with additional foods was 0.01 standard deviations less weight gained (0.15 standard deviations less weight gained to 0.13 standard deviations more weight gained)	-	100 (1 RCT)	⊕⊕⊕◯ MODERATE [3]	The differences in weight change from 4 to 6 months are negligible between the groups
Confidence in breastfeeding (maternal or of those influencing the mother)						This outcome was not reported in a format that could be analysed

*__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; **MD:** mean difference; **RR:** Risk ratio

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

[1] Quasi-random sequence generation (by week of birth) (-1).
[2] Wide confidence interval crossing the line of no effect and small sample size (-1).
[3] Estimate based on small sample size (-1).

DISCUSSION

This review now includes 11 trials in which a total of 2542 healthy breastfeeding infants or their mothers were randomised. There are two time periods in this review. Seven trials related to the first few days after birth and the intervention of additional water, glucose or artificial formula compared with exclusive breastfeeding, with two taking place in the USA and one in each of Spain, Nigeria, Sweden, the UK and the Czech Republic. Four trials focused on three- to six-month-old infants and the intervention of additional foods from three or four months compared with exclusive breastfeeding until six months, with two related trials carried out in Honduras, and one in each of Iceland and the UK, two in the USA, two in the UK and one in each of Spain, Nigeria, Sweden and the Czech Republic.

The trials were very variable in size and showed high heterogeneity, as would be expected due to differences among the trials' interventions and measures of outcomes. The trials extend over a long time span and practices considered normal care in the past, such as additional water in the first few days or additional foods before six months, have been shown not to be best practice. They are included in this review as these older practices still are seen in some places or these beliefs affect information given by those advising new mothers. Care needs to be taken with interpretation of studies where definitions of exclusive breastfeeding were unclear, varied within the trial report, and differed from WHO definitions. Except for the two trials related to allergy, trials were short term and this may mask effects of the interventions on later health.

The control group is healthy infants exclusively breastfeeding to six months of age.

Summary of main results

Additional artifical milk formula to breastfeeding babies in the first few days after birth

In two trials with a similar protocol, giving infants 10 mL of hydrolysed formula via feeding syringe according to a schedule after feeding at the breast in the first few days did not effect the number of infants with any breastfeeding at hospital discharge. although it did show a marginally higher number with exclusive breastfeeding in the 24 hours prior to discharge and in the 24 hours prior to data collection at one week and at three months. Some of the main quality concerns of these two trials include the apparent willingness of the women to be assigned to either exclusive breastfeeding or to supplement breastfeeding, which calls into question what information they had on the value of exclusive breastfeeding and potential increased risks of ill health associated with not exclusively breastfeeding; the use of 5% weight loss as a risk and the entry criteria for the trial, which is within the normal limits of neonatal weight loss; that the control group of exclusively breastfeeding infants were reported as receiving higher amounts of artifical milk during the trial period than the intervention group arising from maternal request and raises questions about what support was available for mothers to achieve exclusive breastfeeding; as well as varying definitions of exclusive breastfeeding. There was no difference in maternal perception of their breastfeeding self-efficacy between the exclusive breastfeeding and the additional artificial formula groups when assessed at one week, which does not appear to support one trial investigators' statement that the intervention of scheduled supplementation would reduce maternal concerns. The intervention of additional artificial milk in the first few days after birth did not show an effect on the incidence of requiring phototherapy. In another study, the finding that cows' milk artificial formula in the first few days before commencing exclusive breastfeeding showed results that indicated these children were less likely to show "obvious or probable symptoms" of allergy (atopic eczema, wheezing, urticaria, gastrointestinal (GI) allergy or multiple allergies) at 18 months should be interpreted cautiously as artificial formula composition changes frequently and formula used in a trial in 1988 may differ considerably from those currently available. The intervention was only for two to three days immediately after birth and many other variables could affect later allergic signs, as well as the lack of diagnostic challenges or other tests performed to confirm that the reported signs of allergy were clinically confirmed.

Additional water or glucose water to breastfeeding babies in the first few days after birth

Trials giving additional water or glucose water to breastfeeding babies in the first few days after birth did not provide evidence that the practice was of benefit to the newborn infant as regards the incidence of fever (the difference of 0.1 degree is likely not to be at a clinically significant level) or effect the risk of bilirubin levels reaching a level needing clinical treatment. Newborn weight change showed, by day three, no significant differences between groups. As might be expected, serum glucose levels were marginally higher in the infants who received glucose supplements in the first 24 hours, though there was no significant difference at 48 hours and there was no evidence of beneficial difference shown in the number of episodes of hypoglycaemia in the first 48 hours. In interpreting the results, there may be the assumption that higher glucose levels are better and thus the exclusively breastfeeding infant is possibly at risk; similarly that higher weight gain is beneficial. However, it could be interpreted that non-exclusively breastfeeding infants with higher glucose levels and weight gains are the infants at possible risk, particularly in relation to longer-term health outcomes related to obesity and diabetes. One trial showed possible risk in that the additional fluids may contribute to a reduction in the duration of breastfeeding as well as highlighting the cost to the hospital involved in giving additional fluids to infants who will not benefit from these fluids. This trial highlighted concerns about the quantity of glucose water used, up to 70 mL/kg/day,

when given based on the mother's or staff perception of the need for the supplement as giving large amounts of water/glucose water may displace nutrients that would be provided by milk resulting in increased weight loss/low weight increase.

Additional foods started at three to four months of age

Starting additional foods early did not show significant difference from the exclusively breastfeeding as regards weight gain; incidence of fever; upper respiratory symptoms of cough, congestion, nasal discharge or hoarseness; or iron deficiency with or without anaemia, during the trial period (up to six months of age). The percentage of days that infants 16 to 26 weeks old had diarrhoea (reported by mother and defined as more than three liquid stools/day) was higher in the exclusive breastfeeding than the additional foods groups in one trial though not in the other trial by the same group. The trialists highlight that the infants in the additional foods groups received commercially prepared jars of food and that the more normal situation of using home-prepared foods from the local culture, with a potentially higher bacterial load, might have shown a higher prevalence of diarrhoea. The trialists also discuss how differences in definitions of diarrhoea may affect their conclusions. Breastfeeding infants normally have stools that are more frequent and softer than infants who are fed on cow's milk feeds or complementary foods. The definition of what is considered abnormal can affect the interpretation of the findings. Relying on maternal diagnosis of infant illness and maternal recall of any illness over the previous three weeks may result in recall bias.

In one trial, parents in the group exclusively breastfeeding for six months had significantly more concerns about their child's development or behavioural status at 18 months and at 30 to 35 months, despite developmental tests showing no differences between groups. Reasons for the parental concern are not discussed and mention is made by the trial investigator of low iron levels contributing to developmental delay, though neither iron deficiency anaemia or developmental delay was found among the children. Expressing this link in the research raises a question: are parents and health workers as well as researchers receiving information from commercial marketing that implies exclusively breastfeeding for six months could result in lack of iron and later developmental concerns?

A recent large trial included in this review examined the effect of early addition to breastfeeding infants of six potentially allergenic foods (from three months of age) on the incidence of food allergy, eczema and food protein enterocolitis syndrome, among many other outcomes. The results, analysed as intention-to-treat, showed no difference between the groups in the duration of any breastfeeding or for any of the allergy outcomes. Only 43% adhered to the complex intervention protocol and a per-protocol analysis indicated the intervention reduced the incidence of allergy. Debate within the allergy research community is continuing including, if there are previous family experiences of allergy, do parents attribute minor behaviours of the infant to allergic reactions and avoid giving the foods, are some of the foods too difficult for immature oral-motor skills, and how much can the protocol vary and still be effective (Wong 2016)?

Overall completeness and applicability of evidence

We applied standard Cochrane methods for our searches, examined references cited in trials, searched for additional publication by previously included trialists, and contacted authors of recent trials for further information and unpublished data to include. Both review authors are employed in areas related to this topic and likely to be aware of research so we are confident this review is a comprehensive representation of the existing body of literature. This topic experiences widespread debate currently, and over past decades and more trials might be expected, however ethical concerns about reducing an infant's acces to their mother's milk or adding a non-human milk protein into a newborn baby's system make these trials difficult to undertake. Past research findings resulted in internationally recognised guidelines for practice clearly supporting exclusive breastfeeding for the first six months and thus funders, parents and research review boards may be hesitant about involvement in trials contrary to these guidelines.

One included study from 1982 (no data for inclusion) examined the effect on intestinal bacteria of the newborn infant of additional glucose water versus exclusive colostrum. It is surprising that more recent trials were not found on the effect of additional fluids and foods versus exclusive breastfeeding on the infant microbiota and effects on later health.

The studies reviewed came from a wide range of countries and are published in English. Breastmilk is readily available and does not involve additional resources such as electricity or technology, or the costs associated with purchasing alternative fluids and food. Evidence not part of the topic of this review indicates there may be negative effects of early additional of non-human fluids which may have illness-associated costs. One older study in this review mentioned the cost of the early fluids additional to mother's milk and one study referred to possible concerns from contamination of the intervention fluids and foods. The costs and safety of interventions are important to include in determining the suitability of an intervention.

Quality of the evidence

The evidence for the comparison of additional early artificial milk versus exclusive breastfeeding was graded as a having a low quality of evidence for any breastfeeding at discharge and three months, maternal self-confidence and very low quality of evidence for allergy symptoms for reasons including unclear definitions of sup-

plement feeds, uncertainty of the impact of recruiting infants with a 5% or greater weight loss and small sample size.

The evidence for the comparison of additional early water or glucose water versus exclusive breastfeeding had low quality of evidence for any breastfeeding at 12 months and weight change at 48 hours of life because of lack of information on sequence generation or allocation concealment and small sample size. The evidence for the comparison of additional early water or glucose water versus exclusive breastfeeding had very low quality of evidence for hypoglycaemia at 12 and 24 hours of life, weight change at 72 hours of life and weight loss (%) at three and five days of age because of one trial with no information on sequence generation or allocation concealment and wide confidence intervals or confidence intervals meeting the line of no effect.

The evidence for the comparison of early additional foods versus exclusive breastfeeding had a low quality of evidence for fever and mean weight change at four to six months due to quasi-random sequence generation, small sample size and wide confidence interval crossing the line of no effect. The remaining outcomes (weight change expressed as a z-score at four to six months, food allergy at one to three years, visible eczema at 12 months (stratified by visible eczema at enrolment) and food protein enterocolitis syndrome) were graded as having moderate quality of evidence because of wide confidence interval crossing the line of no effect and small sample size.

We did not downgrade any of studies for performance bias as due to the nature of the interventions blinding would not have been possible. See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3 for further details.

We assessed each of the 11 studies for risk of bias and found that over half of the studies (n = 7) had a high risk of other biases. We were unable to assess eight studies for selection bias. All but one study (Perkin 2016) achieved the same grade for both random sequence generation and allocation concealment, which are both markers for selection bias. Three studies each were assessed as being low (Flaherman 2013; Jonsdottir 2012; Straň ák 2016) and high (Cohen 1994; Dewey 1999; Lindfors 1988) risk for selection bias, and we could not evaluate four trials (Martin-Calama 1997; Nicoll 1982; Ojofeitimi 1982; Schutzman 1986) for selection bias. Further details are listed in the 'Risk of bias' tables (Characteristics of included studies) and summary graphs of methodological quality (Figure 2; Figure 3).

Three of the 11 included studies provided no information on funding sources in their published papers (Martin-Calama 1997; Ojofeitimi 1982; Schutzman 1986). Support from, or a financial relationship with an infant food manufacturer, or their marketing body, was declared in five trials (Cohen 1994; Flaherman 2013; Jonsdottir 2012; Nicoll 1982; Perkin 2016). The non-standard intervention artifical milk was supplied in pre-filled syringes though it is not stated if these were provided by the manufacturers (Flaherman 2013). Sources of non-commercial support were declared by seven trials (Cohen 1994; Dewey 1999; Flaherman 2013; Jonsdottir 2012; Lindfors 1988; Perkin 2016; Straň ák 2016).

Potential biases in the review process

We applied a search strategy to identify all potential trials. However, although we identified 11 trials, we were unable to extract several relevant outcome data pre-specified in our protocol. Some of these outcome measures were most likely not ascertained during the trial; however, others could have been collected but not reported. For the studies over 10 years since publication we did not contact the primary investigators to obtain any additional data.

Otherwise, to minimise bias, we followed the methodology for systematic reviews outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and customised to this review as described in Methods.

Agreements and disagreements with other studies or reviews

This review did not find any disagreements with the Cochrane review by Kramer which included both observational studies and randomised controlled trials examining exclusive breastfeeding versus earlier introduction of complementary foods (Kramer 2012). This Kramer review formed the basis for the World Health Organization recommendations, and thus numerous other recommendations, that exclusive breastfeeding is recommended for the first six months after birth. A review to systematically evaluate the effect of additional fluids or feedings during the first days of life on the overall breastfeeding duration and rate of exclusive breastfeeding among healthy infants was conducted in 2006 (Szajewska 2006). The Szajewska 2006 review only included one of the trials (Martin-Calama 1997) eligible for inclusion in this Cochrane review and concluded that there is insufficient evidence to form conclusions about the effect of brief exposure to additional food or fluids or both on infant health and the duration of breastfeeding. This review found potential disagreement with the World Health Organization recommendations, and thus numerous other recommendations, in respect of early additional artifical milks versus exclusive breastfeeding. The findings from two trials with the same protocol (Flaherman 2013; Straň ák 2016) present data that would be in disagreement with findings of many other studies (such as those cited in the Background). We found quality concerns in these two trials, as outlined in the review, and we could not recommend that guidance or practice be altered based on their findings.

AUTHORS' CONCLUSIONS

Implications for practice

This review did not find any evidence for disagreement with the recommendation of the World Health Organization and other international health associations (WHO 2003) that, as a general policy exclusive breastfeeding, without additional foods or fluids, should be recommended for the first six months after birth.

Additional fluids and foods may have short- and long-term risks to the infant and parents and health workers should be aware of these risks in order to make an informed decision about the use of additional fluids and foods for the breastfeeding baby.

Care should be taken to provide skilled support from birth to establish milk production and effective milk transfer so as to reduce the risk of weight loss exceeding an established clinical risk level and additional fluids and foods seen as the routine treatment. Pratices and attitudes in hospitals should facilitate evidence-based international recommendations implemented as standard practice to enable exclusive breastfeeding and to protect infants from additional fluids or foods if these are not clinically indicated (UNICEF/WHO 2009).

Implications for research

In the previous version of this review we stated that older trials and "more recent observational studies and theoretical constructs indicate possible negative effects from supplementation of the breastfeeding infant in the first few months, and combined with recommendations from international health authorities to avoid supplementation unless for a clear medical need, it may now be considered unethical to conduct a trial in which an infant is randomised to receive supplements solely for the purpose of the trial (Becker 2011)". There was one trial in the 2011 version and a second trial in this updated review that did provide additional feeds to breastfeeding infants for the purpose of their trial, both using greater than 5% weight loss as the indicator of need for additional feeds, despite this level being within accepted normal weight patterns. The negative reaction to the first trial from professional associations and individual health professionals (Furman 2013; Merewood 2013; Smith 2013; Stuebe 2013) did not appear to affect further associated research conducted on routine scheduled formula supplementation of healthy babies in the first few days after birth without a clinical need and with imprecise definitions of exclusive breastfeeding. It is of concern that this protocol appears to be used in two associated ongoing trials listed in this review thus increasing the risk that these routine supplementation practices and the 5% loss regarded as a clinical risk will come into common use without regard for major limitations of these trials.

Use of precise and internationally accepted definitions of exclusive breastfeeding would improve the quality and comparability of trials, as would information on birth method including maternal intravenous (IV) fluid load and time from birth to initiation of breastfeeding. These variables have been shown to affect infant weight in the first week.

Though not an outcome included in this review, supplementing the breastfeeding infant may have effects on the mother that could include engorgement, mastitis, earlier return of fertility, nutritional status, and maternal use of time as well as maternal mental health and financial effects related to duration of breastfeeding. These maternal aspects could be examined in any future research on this topic. This review did not examine an effect of the method by which any supplement was given, though the use of an artifical teat may affect infant sucking skills, contributing to breastfeeding difficulties as well as introducing a potential source of infection and a potential confounder related to morbidity. This review looked at studies up to the infant age of six months. The addition of non-human milk, other fluids and foods into the infant's immature system may have long-term effects on the gastrointestinal development, metabolic and immunological status of the child (Horta 2007). It would be valuable if in future studies the longer-term effects were also considered.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Cohen 1994

Methods	RCT. 3-arm trial. Parallel design.
Participants	Low-income communities in San Pedro Sula, Honduras. Primiparous, breastfeeding mothers and their infants (n = 152) recruited from public maternity hospitals
Interventions	Trial from 4 to 6 months and longitudinal study of infants from birth to 12 months At 16 weeks, infants assigned to: 1. control (EBF to 26 weeks; no other liquids (water, milk or formula) or complementary food); 2. CFs (introduction of CFs at 16 weeks, with ad libitum breastfeeding); or 3. CFs and maintenance (introduction of CFs at 16 weeks with maintenance of pre-intervention breastfeeding frequency). After 6 months, mothers continued to breastfeed and also fed their infants
Outcomes	Infant weight measured weekly between 16 and 26 weeks and monthly from 7 to 12 months. Infant length measured at 16, 21 and 26 weeks and monthly from 4 to 12 months Infant motor development following 10 motor milestones. Maternal height and weight measured at birth of infant and weight was re-measured according to the infant weight measurement schedule. Maternal supra-iliac and thigh skinfold thickness and circumference at the bust, below the bust, waist and hip were measured at 16, 21 and 26 weeks. Maternal % body fat measured at each time point Breast milk intake measured by test weighing for 48 hours at 4, 5 and 6 months. After this period, breast milk samples were collected for 24 hours and samples were pooled and frozen for later lipid and lactose analysis. For the CF groups, CF intake measured at 19, 24 and 26 weeks Infant morbidity was tabulated at 4 to 6 months and 6 to 12 months. Morbidity prevalence was calculated as % of days ill in each category of illness (diarrhoea, fever and upper-respiratory illness)
Notes	We combined 2 intervention arms with complementary foods into 1 for our analysis of infant weight gain. Original data are: EBF arm n = 50; 1092 g (SD 356 g); 1. complementary food arm n = 47; 1052 g (SD 315 g); 2. complementary food and maintenance arm n = 44; 1004 g (SD 402 g). The additional foods for the trial infants were reported as provided at reduced cost by the Gerber Products Company. Non-commercial funding for the study was provided by the Thrasher Research Fund, WHO, UNICEF Honduras, and Institute for Reproductive Health Washington DC under a funding agreement from USAID

Risk of bias

Bias	Authors' judgement	Support for judgement

Cohen 1994 (*Continued*)

Random sequence generation (selection bias)	High risk	By week of birth (i.e. all infants born in the same week were randomly assigned to the same group)
Allocation concealment (selection bias)	High risk	Participants were not informed of their assignment until they had completed the first (non-RCT) section of the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	152 women entered the intervention trial, 11 (7%) dropped out prior to 26 weeks (9, 1, and 1 in the EBF, CF, and CF-M groups, respectively; P < 0.01) . Reasons for leaving the study between 16 weeks and 26 weeks were reported: 2 had to return to work (both in EBF) and 5 were refused permission to continue participating (4 EBF and 1 CF-M). The other 4 (3 EBF and 1 CF) were excluded because they did not exclusively breastfeed (or introduced other milks in the CF group). Characteristics of non-participants who dropped out at commencement of the intervention trial were similar to those of participants 141 participants completed the study (50 EBF, 47 CF, 44 CF-M). 20% of infants weighed less than 2500 g at birth. The groups were similar in infant birthweight and sex; maternal age, weight, BMI, education, and marital status; and household income. Mothers in the CF-M group were less likely to have received prenatal care than mothers in the 2 other groups
Selective reporting (reporting bias)	Unclear risk	Data on all the outcomes mentioned in the 'Methods' section of the published papers were reported. We did not retrieve the protocol or raw data of the trial and thus did not identify whether outcomes other than those reported within the published papers were collected but not reported on
Other bias	High risk	No power calculation was done to determine the study's sample size

Dewey 1999

Methods	Prospective observational study followed by a randomised intervention trial (from 4 to 6 months). 2-arm. Parallel design
Participants	222 (of which 128 were eligible for the intervention phase of the study) full-term (≥ to 37 weeks' gestation) low birthweight infants (weighing 1500 to 2500 g at birth) from 2 maternity hospitals in San Pedro Sula, Honduras whose mothers (aged ≥ 15 years of age) were willing to exclusively breastfeed for 6 months and were not planning to work outside the home
Interventions	At 16 weeks of age, infants who were still exclusively breastfeeding were randomly assigned to 1 of 2 groups: (1) continued EBF to 6 months, or (2) complementary feeding (CFs) plus breastfeeding from 4 to 6 months, with mothers encouraged to maintain baseline (16 week) breastfeeding frequency
Outcomes	Growth and morbidity from 16 to 26 weeks were assessed for all infants. Morbidity data collected by maternal recall of illness symptoms (weekly) Blood samples collected at 2, 4, 6 months of age. Any infants identified as anaemic, i.e. Hb < 100 g/L, were given iron supplements and re-tested 2 weeks later Daily diary of infants stool frequency and consistency were recorded by the mothers For a sub-sample (n = 63) measurements of breast milk intake and composition and total energy intake at 16 and 26 weeks were completed At 26 weeks, intake of CFs by infants in the complementary feeding plus breastfeeding group was also determined Infant motor development following 10 motor milestones. Maternal height (at time of birth) and weight (weekly). Maternal consumption of any vitamin and mineral supplements were recorded Duration of lactation amenorrhoea. Assessment of attitudes of mothers to EBF. After the intervention phase, infant growth was measured monthly until 12 months of age
Notes	Support from UNICEF and Wellstart International under a grant from USAID; commercial support for the provision of jars of complementary food not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assigned by week of birth (i.e. all infants born in the same week were assigned to the same group)
Allocation concealment (selection bias)	High risk	Participants were not informed of their assignment until they had completed the first (non-RCT) section of the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated for outcome assessors, although appears to be same researchers at all points
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	For RCT part of study n = 128 at 4 months (study commencement). By the end of study, 9 (8 in the EBF group) had dropped out with 119 completing study to 6 months. Mothers in the EBF group dropped out because: they moved away (n = 3), they went back to work (n = 2), they never intended to exclusively breastfeed (n = 1), they felt they were losing too much weight (n = 1). The 1 participant who dropped out of the CF group did so because she did not want to continue There were no significant differences between the 119 participants and the 9 dropouts in infant sex, gestational age, ponderal index, or weight and length gains from birth to 16 weeks, nor in maternal height, BMI, income or prenatal care However, dropouts had significantly lower birth weights, head circumferences, Apgar scores at 5 min, and maternal ages Of those who remained in the study through 6 months, 44% were male, and mean values were 2364 +/- 137 g for birthweight, 23.3 +/- 3.3 kg/m^2 for maternal BMI, and 5.7 +/- 2.7 years for maternal education The sample sizes at 4 and 6 months for the blood indices analysed using frozen samples were smaller than those analysed immediately (Hb, Hct and MCV) because of a robbery (of the freezer with contents) at the Honduras facility near the end of data collection. This resulted in a loss of approximately 30% of the 4-month samples and approximately 30% of the 6-month samples. To determine whether these losses introduced bias, the authors evaluated whether the characteristics of those with lost samples at 4 or 6 months differed from those with complete data in either intervention group. There was little indication that the loss of samples in-

Dewey 1999 (*Continued*)

		troduced bias in interpreting the effect of the intervention. Nevertheless, data were analysed in 2 ways: considering only those with information available at both 4 and 6 months, and considering all samples available at 6 months
Selective reporting (reporting bias)	Unclear risk	Data on all the outcomes mentioned in the 'Methods' section of the published papers were reported. We did not retrieve the protocol or raw data of the trial and thus did not identify whether outcomes other than those reported within the published papers were collected but not reported on
Other bias	Low risk	No issues. "The target sample size was 56 per group, which was based on detecting a difference between groups of ≥15% in weight or length gain between 4 and 6 mo by using SDs for these outcomes for the 28 low-birth-weight infants in our previous study. "

Flaherman 2013

Methods	RCT, 2-arm, parallel design. 2 to 4 days in first week after birth with follow-up to 3 months. Designed to be a pilot to test feasibility USA.
Participants	40 exclusively breastfeeding healthy term infants > 37 weeks' gestation, 24 to 48 hours old, who had lost > 5% birthweight before 36 hours of age were randomly assigned to continue EBF n = 20 (control) or to receive formula supplementation n = 20 (intervention) "Infants were excluded if [at time of enrolment] they had lost > 10% of their birthweight, had received formula or water, required a higher level of care than a Level 1 nursery or had mothers who were, 18 years old, could not speak English or Spanish, or were making mature milk as assessed by a previously validated technique." 2 hospitals California, USA.
Interventions	"Early limited formula (ELF) intervention (10 mL formula by syringe after each breastfeeding and discontinued when mature milk production began) or control (continued exclusive breastfeeding)." Nutramigen infant formula (stated as "extensively hydrolyzed")
Outcomes	Breastfeeding and formula use at 1 week and 1, 2, and 3 months (duration of breastfeeding) Weight nadir in protocol, only weight loss reported (at age not stated) Maternal breastfeeding self-efficacy and maternal satisfaction at 1 week Incidence of febrile illness.

Notes	Further details sought from trialist with some response. Registered as ClinicalTrials.gov Identifier: NCT00952328.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The allocation sequence for randomisation was generated by an independent biostatistician stratified on location; assignments were placed into sealed opaque envelopes by an independent administrative assistant."
Allocation concealment (selection bias)	Low risk	"Immediately after enrolment, a study investigator opened the sequential envelope in the presence of a second investigator and revealed the randomisation arm."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unfeasible to blind participant or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A blinded research assistant assessed outcomes at 1 week and 1, 2, and 3 months." Unfeasible to blind participants or personnel.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1-3 infants were missing data at various follow-up time points according to the published table with no information regarding which group, or if the same participants were missing data at multiple points, or different participants at each point. Information requested from trialist but was not available. Outcomes in trial protocol did not fully match outcomes reported in publication
Selective reporting (reporting bias)	High risk	Lack of definition of breastfeeding and particularly of EBF. The rates of EBF dropped from week 1 to 1 month then increased in the both groups in month 2 and dropped in month 3. This implies the definition of EBF was not in accordance with WHO guidelines. The control group of EBF may have received infant formula as only 53% of this group were exclusively breastfeeding by the end of week 1 and the amount of

		formula used in the control group in the first week was over double the amount used in the intervention group
Other bias	High risk	Protocol as ClinicalTrials.gov Identifier NCT00952328 listed primary outcome as: Is infant receiving exclusively breast milk at 8 days of life, published paper refers to "1 week". Protocol "Both groups will receive intensive lactation support" - published report does not mention "intensive" support Small sample size. Only 62% of those replying (6 out of 40 did not reply) at the start of the intervention had planned to exclusively breastfeed which may have affected their motivation to comply with the allocation. There were more multiparous women in the intervention group than the control group (70% vs 50%) and previous experience of breastfeeding is a well-established predictor of subsequent feeding Effect on weight was an outcome however, the study did not specifically weigh infants; used hospital routine weights, and only reported loss, not gain Inclusion criteria was weight loss of $\geq$ 5% though this is well within the range of normality, and no infant in the study had a medical reason for supplementation. Unclear what was the support provided for breastfeeding, if mothers were instructed regarding how often to feed, to express milk if infant was not feeding well, etc. No information on birth practices that may have affected commencing breastfeeding. No definition of a "feed" thus the instruction to give the 10 mL of supplement "after each feed" could be 8 times, 12 times or more and thus variable quantities consumed. As supplement was given by syringe the infant was not able to refuse the supplement if already content with the amount of breast milk received Funding: supported by grants 5 K12 HD052 and 1K23HD059818-01A1 from the National Institute of Children Health and Human Development. One of the trialists has served as a paid consultant to

		4 companies in the formula industry including the company producing the supplemental formula used in the intervention. Report does not state if formula was supplied by the company or purchased; some participants were provided with small amounts of the formula to continue supplementation for a short time after discharge from hospital ("about 12 ounces" from additional information from trialists)

Jonsdottir 2012

Methods	RCT. 2-arm. Parallel design.
Participants	119 randomly assigned at 4 months. Full-term (≥ to 37 weeks' gestation) 61 were allocated to the CF group and 58 to the EBF group. Although 1 mother-infant pair was incorrectly instructed to group EBF and was therefore analysed in the EBF group, so N = 60 for CF; N = 59 for EBF At a screening visit all mothers stated willing to continue to exclusively breastfeed to 6 months
Interventions	At 4 months of age, infants who were still exclusively breastfeeding were randomly assigned to 1 of 2 groups: (1) continued EBF to 6 months, or (2) CF plus breastfeeding from 4 to 6 months EBF was defined as breastfeeding with no additional liquid or foods other than vitamins and medications
Outcomes	For the CF group, mothers kept a diary to indicate the date that every new food item was added to the infant's diet from the time of enrolment into the study until 6 months of age. A 3-day weighted food record was obtained when the infant reached approximately 5 months and 1 week of age. Energy and nutrient information were calculated For both groups Anthropometric assessment: included infant's weight, length and head circumference. Measured at birth, 6 weeks, and 3, 4, 5 and 6 months of age (converted to z scores using the WHO Infant Growth Standards) Blood samples: obtained to determine iron status. Obtained at 6 months of age - blood for Hb, MCV, RDW, serum ferritin, and TIBC Breast-milk intake: determined by the deuterium dose-to-the-mother method Measures of developmental and behavioural status: assessed at both 18 months and 30 to 35 months with the Parent's Evaluation of Developmental Status (PEDS) questionnaire and the Brigance Screens-II The Jonsdottir trial retrospectively collected information on total duration of breastfeeding for all infants. However, we are unable to present these data as they were combined with data from an additional cohort of infants from a separate national prospective study
Notes	EBF: the use of up to 10 feedings of formula or water during the first 6 months was allowed to avoid having to exclude infants who were otherwise exclusively breastfeeding Clinical Trial Registration: ISRCTN41946519.

	Study was supported by the Primary Health Care organisations in the Reykavik Capital area, Akranes, and Sudurnes, and by the Directors of the participating health centres The study was supported by Mead Johnson and the Eimskip Fund for the University of Iceland. The sponsors of the study had no role in the study design, data collection, data analysis or interpretation, preparation of the report or the decision to submit for publication. None of the authors received honoraria, grants or other forms of payment to produce the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation method was prepared using Jerry Dallal's Tufts-based software, and the trial statistician prepared the provided a computer-generated randomisation code. Assignments were generated by using permuted blocks of 2 and 4, with the sequence presented in random order
Allocation concealment (selection bias)	Low risk	Assignments were accessed by using a password-protected web-based application, after eligibility criteria were confirmed. Assignments were generated by 1 person (a nurse) who was not involved in any other aspect of the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses who collected data on complementary food intakes and anthropometric outcomes were not blinded to participant group status, but all mass spectrometric analyses and isotopic modelling were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 119 (n = 61 in CF group, n = 58 in EBF group) mother-infant pairs were recruited, of whom 100 completed the trial protocol CF group 10 pairs discontinued the intervention (n = 3 infant did not receive CF; n = 3 infant did not want CF; n = 1 mother stopped breastfeeding; n = 2 mother did not have time to finish study; n = 1 mother not contacted after randomisation) EBF group 9 pairs discontinued the intervention (n = 7 infant received CF before 6 months; n = 1 mother wanted to leave study; n = 1 illness in family Also, after randomisation, 1 mother who was randomly assigned to the CF group was incorrectly instructed to

Jonsdottir 2012 (*Continued*)

		the EBF group. The primary analysis was conducted with this mother included in the EBF group (n = 50 EBF, 50 CF) but reported outcomes for the baseline analyses with the participant in the CF group (n = 49 EBF, 51 CF) The authors state that they were not able to test whether those who dropped out of the study were those with lower breast milk intakes - i.e. potentially a self-selected group
Selective reporting (reporting bias)	High risk	In protocol states under secondary outcomes: "3. Occurrence of upper respiratory infections and diarrhoea episodes (dichotomous variables)" But in Wells paper states "Finally, our study was designed to evaluate growth and energy intake and not other issues such as development of dietary preferences, mineral status, or effects on health such as diarrhoea and allergy"
Other bias	Low risk	Stated that the study sponsors (Mead Johnson and the Eimskip Fund of the University of Iceland) had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication. None of the authors declared a conflict of interest "Our sample size of 50 mother-infant pairs who completed their participation in each group (n = 100) was based on primary outcome of the study, breast-milk intake. That sample size allowed for the detection of an effect size of 0.6 between the 2 groups with 5% significance level (2-sided comparison) and 80% power

Lindfors 1988

Methods	Quasi-RCT. Sweden.
Participants	Term infants (37-42 gestational weeks') with no major initial neonatal problems born and a birthweight between -1 and -2 SDs between June 1981 and January 1983 in Danderyd Hospital, Sweden 112 infants were assigned to the intervention group (infant formula) and 109 infants had data available for analysis at 18 months. 104 infants were assigned to the breastfeeding group and 98 infants had data available for analysis at 18 months
Interventions	Adapted cow milk formula (Milkotal®). This was first given when the infants were 6 hours old and the amounts given were increased every 4 hours until the infant was taking 60 mL per meal. The formula was gradually withdraw when "the mother's breastmilk production started"
Outcomes	Allergy symptoms (atopic eczema; wheezing; urticaria; GI allergy; multiple allergies)

Lindfors 1988 (*Continued*)

Notes	Outcomes are based on paediatricians assessment but no diagnostic tests were performed. Follow-up assessments occurred at 3, 6 and 18 months but it is not stated if outcomes are incidence or prevalence. We were unable to contact authors to address any of our queries related to their study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-RCT "Following a predetermined protocol,the maternity wards changed their feeding routine the first day of every other month between breastfeeding and early feeding with an adapted cow milk formula"
Allocation concealment (selection bias)	High risk	No allocation concealment took place - hospital staff were aware of the allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Publised paper states that paediatricians at the child welfare clinics who did the follow-up "were unaware of the feeding regimen". As part of the study assessment included taking a full feeding history from birth they may have been told by the parents if the child had received the intervention formula
Incomplete outcome data (attrition bias) All outcomes	Low risk	F = 112 and B = 104 at start = 216. At 18 months F = 109 and B = 98 = 207. Loss F = 3 B = 6 Followed-up at 5 years of age 183 of the 207 children. Loss 24 F = 95 (-14) B = 88 (-10)
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods are reported. No protocol or raw data available
Other bias	High risk	No evidence that power calculation was undertaken to determine sample size "when the mother's breastmilk production started" - does this mean Lactogenesis II or colostrum? "Both groups were breastfed as soon as the mother's lactation started" - did breastfeeding group get any water/glucose water or other fluids? Published paper refers to the examination of feeding originally was started "in order to reduce the starvation period for these infants" which suggests either babies did not have access to colostrum or the value of colostrum was not recognised in the maternity unit High number of outcome assessors working independently. Diagnosis of allergy based on clinical criteria with no lab testing at

Lindfors 1988 (*Continued*)

		18 months A family history of allergy was higher in the breastfeeding group than in the early artifical formula group. "In the F-group 31 children (29%) had a single and 19 (17%) a double heredity. In the B-group 39 infants (40%) had a single and 18 (18%) a double family history of allergy." Non-commercial funding was reported in the follow-up paper.

Martin-Calama 1997

Methods	RCT. 2-arm trial. Parallel design.
Participants	Full-term newborns weighing between 2599 g to 4000 g (n = 180). Vaginal deliveries only, who had no congenital abnormalities and who represented no risk factors for hypo- or hyperglycaemia. General Hospital, Teruel, Spain
Interventions	Group 1 called "glucose water" group, received 5% glucose *ad libitum* from a bottle for the first 3 days of life in addition to breastfeeding. Group 2, the "non glucose water" group, was not given glucose water or any other type of alternative solution to human milk
Outcomes	Weight change (6, 12, 24, 48 and 72 hours of life). Serum glucose levels (6, 12, 24 and 48 hours of life). Rectal temperature (every 6 hours for the first 72 hours of life). The maximum and minimum values during period of observation were used in the final analysis After discharge no contact for 5 months. Then telephone interview determined duration of EBF, duration until introduction of infant formula, and duration until complete weaning were recorded. Time points of 4, 8, 12, 16 and 20 weeks were used
Notes	We have estimated from the graph in the published report the percentage of mothers breastfeeding at each time period (see Table 1) and calculated the number breastfeeding at each time period from these estimates No information on funding sources in the published paper.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Divided randomly into 2 groups."
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.

Martin-Calama 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	N = 180 (90 in each group). 3 children from the non glucose water group and 7 from the glucose water group were ineligible because of missing data or because it was impossible to assure correct transcription of data. Therefore 10 excluded = 5.5%
Selective reporting (reporting bias)	Unclear risk	Data on all the outcomes mentioned in the 'Methods' section of the published papers were reported. We did not retrieve the protocol or raw data of the trial and thus did not identify whether outcomes other than those reported within the published papers were collected but not reported on
Other bias	Unclear risk	Some information on partial or EBF was obtained via telephone conversations (maternal recall of illness symptoms) and this is open to recall bias "Sample size for this study was calculated on the babies of the least exact quantitative variable (blood glucose), with a 95% conference level and an exactness of ± 1SD. Under these conditions, the minimum size required for the sample was 162. To cover the possibility of attrition, the sample was increased by 10% to 180 cases."

Nicoll 1982

Methods	RCT. 3-arm trial. Parallel design.
Participants	Primiparous mothers intending to breastfeed their full-term infants. Intending to be in hospital (London, UK) for 5 days after delivery. 49 originally randomised
Interventions	3 groups: water supplement (n = 14); glucose supplement (n = 17); no supplement (n = 16)
Outcomes	Infant weight (days 1, 3 and 5). Plasma bilirubin (day 6). Volume of supplement taken per day per kilo of baby's birthweight (mL/kg/day) Average weight gain per breastfeed (mg/kg of baby's birthweight)
Notes	Weight loss data for glucose and water supplement arms have been combined for our analysis 2.7. We converted the SEs presented in the original paper to SDs Original data are mean and SE: 1. % weight loss from baby's birthweight; 2. EBF 6.0 (0.5) day 3 and 4.3 (0.6) on day 5;

	3. water supplement 5.9 (0.4) day 3 and 4.2 (0.6) on day 5; 4. glucose supplement 4.1 (0.4) day 3 and 4.0 (0.5) on day 5. Plasma bilirubin data from the glucose and water supplement arms have been combined for our analysis 2.8 Original data are mean and SE: 1. EBF 67.7 (6.7) umol/L; 2. water supplement 93.5 (13.8) umol/L; 3. glucose supplement 80.8 (8.8) umol/L. The additional artifical feeds were "kindly supplied by Wyeth Laboratories"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly allocated" to 1 of 3 groups (no supplement (n = 17); glucose supplement (n = 17), water supplement (n = 15))
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 mother/baby pairs defaulted from the 'no supplement' group because their babies were "too hungry" and were replaced by further randomised pairs. 2 infants were later excluded from the study because of: rhesus incompatibility (n = 1) and ABO incompatibility with positive haemolysins (n = 1). This reduced numbers in each group to: no supplement (n = 16); glucose supplement (n = 17); water supplement (n = 14)
Selective reporting (reporting bias)	Unclear risk	Data on all the outcomes mentioned in the 'Methods' section of the published papers were reported. We did not retrieve the protocol or raw data of the trial and thus did not identify whether outcomes other than those reported within the published papers were collected but not reported on
Other bias	High risk	No evidence that a power calculation was undertaken to determine sample size

Ojofeitimi 1982

Methods	RCT. 2-arm trial. Parallel design.
Participants	180 neonates delivered between October 1980 and January 1981 in 2 local maternity centres in Ile-Ife, Oyo State, Nigeria were randomised. Criteria for selection were that birthweight be above 2.50 kg, no sign of congenital malformation, that mothers experienced uncomplicated birth with membrane rupture less than 24 hours prior to delivery, and no manifest sign of physical exhaustion or sickness after delivery to prevent them from performing their maternal responsibilities to the neonates 105 kept strictly to instructions (60 (57%) on colostrum regimen and 45 (43%) on glucose water)
Interventions	1 group received glucose water feedings and the other colostrum. The mothers were told to keep strictly to these feeding regimens for the entire 3-day stay at the maternity centre
Outcomes	Stool specimens (2 daily) analysed for bacterial counts. Bacterial counts in samples of colostrum and glucose water.
Notes	Did not report any data that were eligible for inclusion in the review no information on funding sources in the published paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned at birth to two groups...."
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participation was voluntary, and those mothers who failed to adhere were excluded from the study Of the 180 mothers chosen for the study, 105 kept strictly to the instructions. 60/105 were on the colostrum regimen (57%) and 45 were on glucose water (43%)
Selective reporting (reporting bias)	Unclear risk	Data on all the outcomes mentioned in the 'Methods' section of the published papers were reported. We did not retrieve the protocol or raw data of the trial and thus did not identify whether outcomes other than those reported within the published pa-

Ojofeitimi 1982 (*Continued*)

		pers were collected but not reported on
Other bias	High risk	No evidence that a power calculation was undertaken to determine sample size

Perkin 2016

Methods	RCT. 2-arm trial. Parallel design.
Participants	n = 1303 eligible infants enrolled at 3 months from a general (not an "at risk" population) . Intervention group 652 randomised and ITT analysis for 567; control group 651 randomised and ITT analysis for 595, "recruited to the study from those who responded to a flyer mailed to parents of young infants throughout England and Wales". Tested at enrolment for allergy sensitisation Inclusion criteria: Exclusively breastfeeding at enrolment, 37+ weeks' gestation, singleton birth, no major health concerns, not planning to move from the United Kingdom for the duration of the study Exclusion criteria:"Infants who had consumed anything other than breast milk or water since birth, were part of multiple births, were born prematurely, had any serious medical condition, or were participating in other medical research were not eligible for enrolment. A current household member with a food allergy was not an exclusion criterion."
Interventions	To determine whether the early introduction of common dietary allergens from 3 months of age in exclusively breast-fed infants in the general population would prevent food allergies than those in infants who were exclusively breast-fed for approximately 6 months. "Between 13 and 17 weeks of age, enrolled infants were randomly assigned to either the SIG or the early introduction group (EIG)." (Early Introduction Group/EIG): at 3 months infants were introduced to cow's milk and then the following foods (cooked hen's egg, peanut, sesame, whitefish) in a randomised sequence and then the last food introduced was wheat and no wheat before 4 months. Trial recommendation was 2 to 4 g of the food protein per week by 6 months Control/Comparison intervention (Standard Introduction Group/SIG): exclusively breast-fed to approximately 6 months of age. After 6 months of age, the consumption of allergenic foods was allowed according to parental discretion Both groups "Parents completed an on-line questionnaire monthly to 12 months and then every 3 months to 36 months. Parents reported any atopic symptoms in their children and any adverse events (serious and non-serious) through the online questionnaire. "
Outcomes	Duration of any breastfeeding. Eczema (visible) at 12 months. Prevalence of "food allergy" to 1 or more foods between 1-3 years of age Adverse events including gastrointestinal events, colic, respiratory effects, growth, hospitalisation for any reason, and morbidity for any reason and many other conditions and details are reported in the supplementary appendices available on-line (data not suitable for analysis and summary reported descriptively. Trialists replied that more publications were likely to arise from this large trial)

Notes	EBF definition allowed water. Supported by grants from the Food Standards Agency and the Medical Research Council, by the NIHR Biomedical Research Centre, which is based at Guy's and St. Thomas' NHS Foundation Trust and King's College London, and by a National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's and St. Thomas' NHS Foundation Trust and King's College London. Also supported by an NIHR Clinician Scientist Award (NIHRCS/01/2008/009) to Dr Flohr. The clinical trials unit is supported in part by the National Peanut Board, Atlanta

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reply from trialists: "Done via ALEA randomisation software"
Allocation concealment (selection bias)	Unclear risk	Reply from trialists: "There was no blinding in the study team and the participant's GP was notified of the allocation. The exception to this was the double blind placebo controlled food challenge that some participants underwent at the 3 year visit"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reply from trialists: "No blinding. Outcome was based upon objective measures of sensitisation (skin prick test results). Food allergy at one year and beyond was determined by the gold standard measure, the double blind, placebo controlled food challenge. This also has strict, set criteria that must be objectively met in order to be deemed positive"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"43 participants in the standard-introduction group and 69 participants in the early-introduction group withdrew voluntarily from the study. Reasons given were as follows: concerns about the blood tests (SIG 0, EIG 2), emigration (SIG 10, EIG 12), expenses (SIG 1, EIG 1), family health issues (SIG 3, EIG 0) , family issues (SIG 2, EIG 4), no reason given (SIG 11, EIG 16), lost contact with family (SIG 15, EIG 28), too far to travel for study assessments (SIG 0, EIG 1) and unhappy participating in the study (SIG 1, EIG 5)." "Only 31.9% (208/652) of all the enrolled early-introduction group participants were primary outcome evaluable and adhered to the protocol ver-

Perkin 2016 (*Continued*)

		sus 80.5% (524/651) in the standard-introduction group." With detailed explanation reported in NEJM appendix
Selective reporting (reporting bias)	Low risk	Protocol published and very extensive appendices on-line with additional data
Other bias	Unclear risk	Adherence to protocol was low in the intervention group (43%). Triallists also reported the per-protocol results/dose response analysis as well as the ITT. Reasons for low adherence require more exploration rather than assume per-protocol results are more true than ITT and not a reverse causality effect States no commercial funding. Clarification from trialists: "The trial has 80% power to detect a 50% relative reduction in the absolute prevalence of food allergy by three years of age (from 8% in the SIG to 4% in the EIG) assuming a 15% drop out rate"

Schutzman 1986

Methods	RCT. 2-arm trial. Parallel design.
Participants	Healthy term neonates (n = 136) in the first 3 days after birth 78 babies nursed exclusively on demand, and 58 babies received supplemental water in addition to on-demand nursing This study was performed in a maternity hospital in Philadelphia, Pennsylvania at which the patient population is highly motivated to breastfeed
Interventions	Exclusive on-demand breastfeeding versus on-demand nursing plus supplemental water. The choice of sterile water or 5 % glucose water was left to the mother
Outcomes	Mean total amount of water ingested by the supplemented group prior to the arrival of true milk The time in hours when true milk first "came in" was recorded for each mother as it occurred
Notes	Did not report any data that were eligible for inclusion in the review No information on funding sources in the published paper.

Risk of bias

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

Schutzman 1986 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reference to dropouts reported.
Selective reporting (reporting bias)	Unclear risk	Data on all the outcomes mentioned in the 'Methods' section of the published papers were reported. We did not retrieve the protocol or raw data of the trial and thus did not identify whether outcomes other than those reported within the published papers were collected but not reported on
Other bias	High risk	No evidence that a power calculation was undertaken to determine sample size

Straňák 2016

Methods	RCT. 2-arm trial. Parallel design.
Participants	Total number randomised: 52 randomised per group, data available for 50 per group. Inclusion criteria: "Infants were eligible for randomisation when their weight loss was equal to or greater than 5 per cent between 24th and 48th hour of life. Only healthy, singleton, appropriate for gestational age (AGA) term neonates, born after uncomplicated pregnancy and delivery, who had no severe congenital defects were enrolled. Mothers of the included infants were planning to breastfeed for a long time and all were Czech citizens. …All mothers involved in the study were planning and wishing to breastfeed over long term" Exclusion criteria: mothers with serious complications (hypertension, diabetes, systemic diseases, drug abuse) or using therapy that might affect breastfeeding (antidepressants) were excluded "The study was conducted at the Institute for the Care of Mother and Child in Prague. Patients were recruited from the 1st of April 2014 until the 29th of August 2014. Follow up was completed on the 27th of February 2015."
Interventions	Experimental intervention: "Infants in the controlled limited formula group (CLF-intervention group) were given a set volume of 10ml of formula (HIPP NE, HIPP Inc., Germany) after each breastfeed until adequate milk production began" Control/Comparison intervention: "Infants in the standard approach group (SA-control group) were exclusively breastfed. Supplemental feeds were administered only in indicated cases. This included excessive weight loss (more than 10% of birthweight),

	irritability of the newborn, in terms of unsettling cry and hungry behaviour, and on mothers specific request. Infants in the control group, if requiring supplemental feeding, were given breastmilk from the breastmilk bank or formula according to the mothers' choice. All formula feeds were always given using the syringe-technique." All infants were weighed daily while in hospital.
Outcomes	1. Any breastfeeding at discharge (binary outcome) 2. EBF at discharge (binary outcome) 3. Any breastfeeding at 3 months (binary outcome) 4. EBF at 3 months of age (binary outcome) 5. Breastfeeding at 6 months of age (binary outcome) 6. EBF at 6 months of age (binary outcome) 7. Percentage of weight loss during hospitalisation (continuous outcome) 8. Phototherapy in hospital or home setting if required, absence or presence, and if present, duration (days) "all participants have been regularly checked for hyperbilirubinaemia as according to standard hospital guidelines. Levels of bilirubin above 200 umol/l have been recorded, as per standard hospital guidelines levels of serum-bilirubin were measured and all cases requiring phototherapy noted."
Notes	Additional information provided by trialists. Supplemental data provided with publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using the sealed envelope technique and randomization with permuted blocks, we randomly assigned 104 mother-infant pairs to either controlled limited formula group (CLF) or standard approach group (SA). The randomization sequence was generated and the sealed envelopes in blocks of 8 were prepared by the hospitals' administration office staff."
Allocation concealment (selection bias)	Low risk	Reply from trialist: "the group allocation was not stated on the day-to-day medical records of the infants, clinicians were not necessarily aware about group allocation, unless told by the mother"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of intervention this was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A research nurse who was blinded to group allocation assessed outcomes during a personal interview at discharge and by a telephone-interview at 3 and 6 months of the infants' age."

		Reply from trialist: "those carrying out analysis of data were blinded as to group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropped out from each group and reasons were reported.
Selective reporting (reporting bias)	Unclear risk	Measured and recorded clinical outcomes that were not pre-determined as study outcomes in the registered protocol
Other bias	High risk	No information on overall hospital maternity population and cannot assess for selection bias Publication implies that protocol was written and registered *after* the trial finished. Unclear definitions. Definitions of EBF varied. Trialists replied: "The definitions varied in the time of data collection and the length of time considered for exclusive breastfeeding. Data collection "during hospitalization" considered the whole time from study enrolment to discharge from hospital. Only newborns who have not received any supplement during the entire time of this period were classified as exclusively breastfed. Data collection "at the point of discharge" was performed at the time of discharge home and babies were considered as exclusively breastfed if no supplement was given for at least 24 hours with adequate weight gain.... Mothers were interviewed at the time point of 3 and 6 months of age of their infant...Infants were classified as exclusively breastfed if no supplement formula was given for at least 24 hours." Review authors queried the definition of a "feed". It is common for infants in the first few days to go to the breast 10-12 or more times in 24 hours; if the infant went to the breast 12 times, did the infant get 12 supplements of 10 ml? Trialists replied: "Breastfeeding on demand is supported within our hospital and was enabled for all unless the mother wished otherwise, however newborns in the CLF group only received supplemental feed of 10 ml after breastfeeding every 3 hours, i.e. 8 times in 24 hours" Review authors queried: what was the definition of 'adequate milk production' and who decided that 'adequate milk production' had started? Trialists replied: "Mothers were checked for expressing milk and adequate milk production each day by experienced specialised nurse, although this was not done

		quantitatively" Review authors queried Why was weight loss of 5% used? Trialists replied: "As per the standard guideline of our hospital, weight loss of >10% of birth weight is considered as excessive and measures to prevent risk of dehydration are taken including begin of supplemental formula feeds. Thus weight loss of ≥5% of birth weight at the age of 24-48 hours was considered most suitable as inclusion criterion to select newborns who may be at risk, yet who are still within "normal limits" for physiological weight loss that does not strictly require intervention" Trialist replied that artificial formula filled syringes were not provided by manufacturer and prepared in the maternity unit. The published paper lists funded by PRVOUK32. The Charles University Research Development Schemes "For the given effect size (population proportions of 0.95 versus 0.75) and alpha (0.052-tailed) with power of 0.80, the estimated sample sizes are 49 in each group. This means that 80% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the two population proportions are equal."

B: breastfeeding
BMI: body mass index
CF: complementary foods
CF-M: complementary foods and maintenance
EBF: exclusive breastfeeding
GI: gastrointestinal
F: cow milk formula
Hb: haemoglobin
Hct: haematocrit
MCV: mean corpuscular volume
ITT: intention-to-treat
min: minutes
RCT: randomised controlled trial
RDW: red blood cell distribution width
SD: standard deviation
SE: standard error
SF: solid food

TIBC: total iron-binding capacity
USAID: United States Agency for International Development
WHO: World Health Organization

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

Study	Reason for exclusion
Bannert 1995	No exclusively breastfeeding group.
Cameron 2015	Intervention is counselling to affect timing of introduction of complementary foods and not addition of foods/fluids
Collins 2004	Preterm infants only (23 to 33 weeks).
Corchia 1985	No exclusively breastfeeding group.
Cronenwett 1992	No exclusively breastfeeding group.
De Carvalho 1981	Not randomised or quasi-randomised. Babies on 1 ward received water supplementation and those on another 2 wards did not. The admission of babies and mothers to the 3 wards was dependent upon availability, but not regarded as random allocation
de Jong 1998	Intervention did not have an exclusively breastfeeding arm.
de Oliveira 2012	Intervention was not the addition of foods/fluids. It was "to evaluate the efficacy of counselling about breast-feeding and complementary feeding in preventing the introduction of non-breast milk and complementary foods in the first 6 months"
Du Toit 2015	Intervention did not have an exclusively breastfeeding arm.
Flaherman 2011	Refers to infants needing treatment for a medical condition, not well infants
French 2012	Mix of breastfeeding and artificial feeding. No exclusively breastfeeding group. Evaluating guidance on infant feeding behaviours
Gray-Donald 1985	No exclusively breastfeeding group.
Howard 2003	Treatment group included preterm babies (36 to 42 weeks).
Juvonen 1996	Group was fed donor human milk not exclusive breastfeeding.
Kearney 1990	No exclusively breastfeeding group.
Kimani-Murage 2013	Intervention was counselling to affect timing of introduction of complementary foods and not addition of foods/fluids
Krebs 2013	Infants were assigned at 5 months to receive 1 of 3 types of complementary foods. Not comparing exclusively breastfeeding under 6 months
Ly 2006	No exclusively breastfeeding group.
Marinelli 2001	Preterm infants only (34 weeks or less).

(*Continued*)

Mosley 2001	Treatment group included preterm babies (32 to 37 weeks).
Olaya 2013	Infants were assigned at 6 months to receive 1 of 2 types of complementary feeding. Not comparing exclusively breastfeeding under 6 months
Rosegger 1985	No exclusively breastfeeding group.
Rosegger 1986	No exclusively breastfeeding group.
Saarinen 1999	Unclear randomisation; may not have randomised control group
Sachdev 1991	No exclusively breastfeeding group.
Schiess 2010	Observational study comparing 2 formula groups.
Schmitz 1992	No exclusively breastfeeding group.
Schubiger 1997	No exclusively breastfeeding group.
Simondon 1996	No exclusively breastfeeding group.
Ziegler 2011	Review of 3 studies of the research group comparing 2 types of cereal introduced at 4 months. No exclusive breastfeeding group

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

Flaherman 2014

Trial name or title	Early limited formula for treating lactation concerns (ELF)
Methods	RCT, parallel assignment, single-blind (outcomes assessor).
Participants	Inclusion criteria 1. Full-term, healthy singleton infant (≥ 37 0/7 weeks gestational age) in "well newborn nursery" 2. Exclusively breastfeeding (has not received any feedings other than breast milk) 3. Infant is 18-72 hours old 4. Infant has weight loss of ≥ 75th percentile on delivery mode specific nomogram documented at 12-72 hours of age 5. English-speaking mother Exclusion criteria 1. Mothers or infants for whom breastfeeding is not recommended by the clinical team 2. Mothers who have already begun to produce mature breast milk 3. Any formula or water feeding prior to enrolment 4. Infants who have already lost ≥ 10% of their birthweight 5. Family with no active telephone number (home or cellular) 6. Plan for infant adoption or foster care

Flaherman 2014 (*Continued*)

	7. Mothers < 18 years of age 8. Infant receiving scoring for Narcotic Abstinence Syndrome
Interventions	Standard Care: continue exclusive breastfeeding unless otherwise directed by a healthcare provider Experimental: early Limited Formula-10 (mL) Nutramigen fed to baby by syringe after each breastfeeding and discontinued at the start of mature milk production
Outcomes	Length of breastfeeding duration (follow-up to 12 months); Maternal State Trait Anxiety Inventory, Edinburg Postnatal Depression Scale, Breastfeeding Self-Efficacy Scale, Satisfaction with Quality of Care, Infant Satisfaction and Satiety Subscale (all 1 month), health care utilisation (1 month), formula use (6 months)
Starting date	December 2014. Estimated completion date June 2017.
Contact information	Valerie Flaherman, MD, MPH flahermanv@peds.ucsf.edu Michelle Rait, RN raitm@peds.ucsf.edu
Notes	Sponsor and collaborators: University of California, San Francisco, Milton S. Hershey Medical Center, HRSA/Maternal and Child Health Bureau ClinicalTrials.gov Identifier NCT02313181.

Kair 2014

Trial name or title	Rx milk study of donor milk supplementation to improve breastfeeding outcomes
Methods	RCT, parallel assignment, open-label.
Participants	Inclusion criteria 1. Gestational age greater than or equal to 37 weeks 2. Weight loss greater than or equal to 5% (rounded to nearest whole %) of birthweight in the first 36 hours after birth 3. Chronological age of 24-48 hours old at the time of study enrolment Exclusion criteria 1. Twins and higher level multiples 2. Infant has congenital or chromosomal anomalies that may affect feeding, diagnosed prior to study enrolment 3. Mother incarcerated 4. Mother's age < 18 years 5. Mother reports mature milk production prior to study enrolment 6. Mother does not speak English 7. Infants offered > 1 supplemental feeding of formula or donor milk 8. Weight loss greater than 10%
Interventions	Control: exclusive breastfeeding. Intervention: "Infants in this arm will continue to breastfeed and will be given 10 ml of donor breast milk by syringe after each breastfeeding until their mother's milk "comes in." (until the onset of lactogenesis II)"
Outcomes	Any formula use at 1 week of age, any formula intake within the last 24 hours, exclusive breastfeeding (at 1 month, 2, month, 3 month), any breastfeeding (at 1 week, 1 month, 2, month, 3 month)

Kair 2014 (*Continued*)

Starting date	July 2014. Estimated completion date June 2016.
Contact information	Laura R Kair, MD laura-kair@uiowa.edu Gretchen Cress, RN gretchen-cress@uiowa.edu
Notes	Sponsors: University of Iowa, Children's Miracle Network, The Gerber Foundation. Study Director: Valerie J Flaherman ClinicalTrials.gov Identifier NCT02221167.

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breastfeeding duration	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Any breastfeeding at discharge	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.08]
1.2 Exclusive breastfeeding in 24 hours prior to discharge	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.00, 1.24]
1.3 Exclusive breastfeeding at 1 week (previous 24 hours)	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.09, 2.68]
1.4 Exclusive breastfeeding at 3 months (previous 24 hours)	2	138	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.15, 1.77]
1.5 Any breastfeeding at 3 months	2	137	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.05, 1.41]
2 Allergy symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infants with allergy symptoms at 18 months of age	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.91]
3 Incidence of fever	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.36]
4 Maternal self-confidence - Modified breastfeeding self-efficacy score at 1 week	1	39	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.34, 0.54]
5 Phototherapy in hospital or home	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]

Comparison 2. Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breastfeeding duration	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Any breastfeeding at 4 weeks	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.73, 0.94]
1.2 Any breastfeeding at 8 weeks	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.96]
1.3 Any breastfeeding at 12 weeks	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.53, 0.87]
1.4 Any breastfeeding at 16 weeks	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.49, 0.87]
1.5 Any breastfeeding at 20 weeks	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.95]
2 Maximum temperature (ºC)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 72 hours	1	170	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.19, -0.01]
3 Minimum temperature (ºC)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

3.1 At 72 hours	1	170	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.18, -0.02]
4 Episodes of hypoglycaemia (glycaemia < 2.2 mmol/L)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 At 6 hours of life	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.08, 2.10]
4.2 At 12 hours of life	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.20]
4.3 At 24 hours of life	1	170	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.27, 9.17]
4.4 At 48 hours of life	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.29]
5 Mean capillary blood glucose levels of infants (mmol/L)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 At 6 hours of life	1	170	Mean Difference (IV, Random, 95% CI)	0.29 [0.02, 0.56]
5.2 At 12 hours of life	1	170	Mean Difference (IV, Random, 95% CI)	0.47 [0.24, 0.70]
5.3 At 24 hours of life	1	170	Mean Difference (IV, Random, 95% CI)	0.34 [0.08, 0.60]
5.4 At 48 hours of life	1	170	Mean Difference (IV, Random, 95% CI)	0.24 [-0.03, 0.51]
6 Weight change (loss) (g)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 At 6 hours of life	1	170	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-13.24, -0.76]
6.2 At 12 hours of life	1	170	Mean Difference (IV, Fixed, 95% CI)	-11.5 [-21.29, -1.71]
6.3 At 24 hours of life	1	170	Mean Difference (IV, Fixed, 95% CI)	-13.40 [-26.37, -0.43]
6.4 At 48 hours of life	1	170	Mean Difference (IV, Fixed, 95% CI)	-32.5 [-52.09, -12.91]
6.5 At 72 hours of life	1	170	Mean Difference (IV, Fixed, 95% CI)	3.0 [-20.83, 26.83]
7 Weight loss (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Day 3	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-2.24, 0.18]
7.2 Day 5	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.86, 0.46]
8 Maximum serum bilirubin levels umol/L	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Day 6	1	47	Mean Difference (IV, Fixed, 95% CI)	18.84 [-1.35, 39.03]

Comparison 3. Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever (% of days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 4 to 6 months	1	119	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.40, 2.00]
2 Cough (% of days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 4 to 6 months	1	119	Mean Difference (IV, Fixed, 95% CI)	3.10 [-4.52, 10.72]
3 Congestion (% of days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 4 to 6 months	1	119	Mean Difference (IV, Fixed, 95% CI)	3.60 [-3.41, 10.61]
4 Nasal discharge (% of days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 At 4 to 6 months	1	119	Mean Difference (IV, Fixed, 95% CI)	4.20 [-1.13, 9.53]
5 Hoarseness (% of days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 At 4 to 6 months	1	119	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.84, 2.04]
6 "Food allergy" to one or more foods between 1-3 years of age	1	1162	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.25]
7 Visible eczema at 12-month visit stratified by visible eczema at enrolment	1	284	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.51, 1.44]

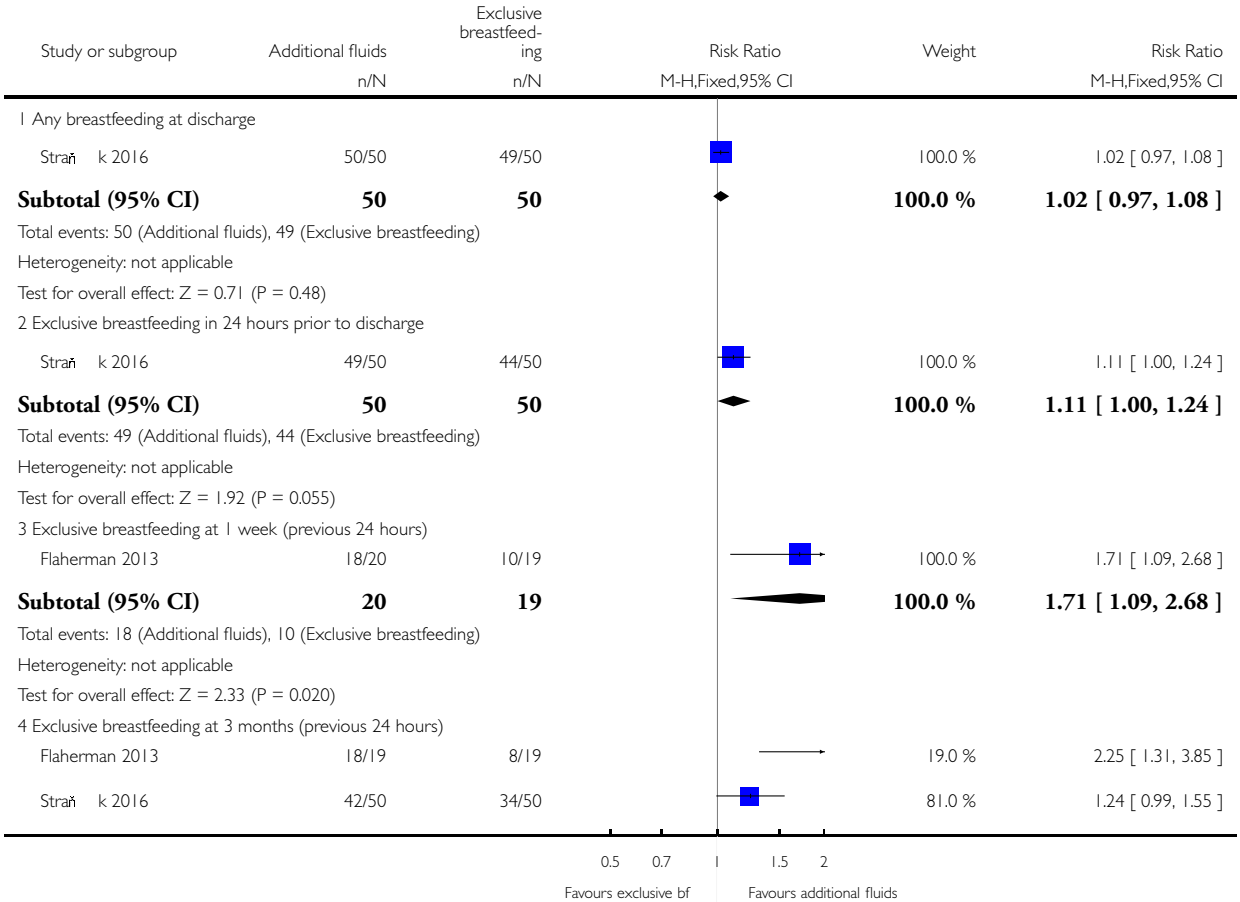
8 Food protein enterocolitis syndrome positive response to challenge (number of children)	1	1303	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.18, 22.04]
9 Weight change (gain) (g)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 At 4 to 6 months	2	260	Mean Difference (IV, Fixed, 95% CI)	-39.48 [-128.43, 49.48]
10 Weight change (z score)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 4 to 6 months	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.15, 0.13]

Analysis 1.1. Comparison 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants, Outcome 1 Breastfeeding duration.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants

Outcome: 1 Breastfeeding duration



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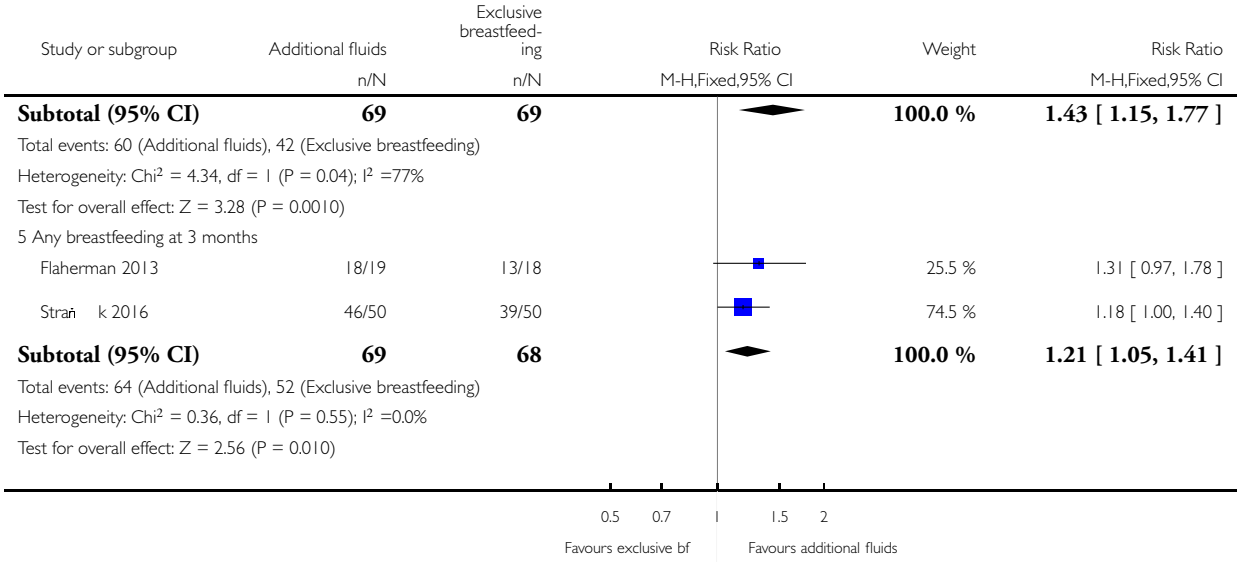
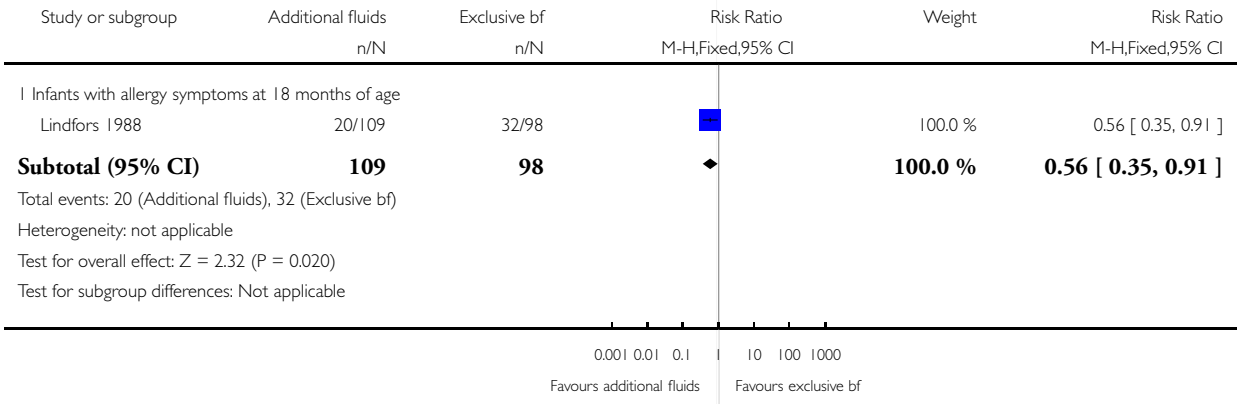


Analysis 1.2. Comparison 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants, Outcome 2 Allergy symptoms.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants

Outcome: 2 Allergy symptoms

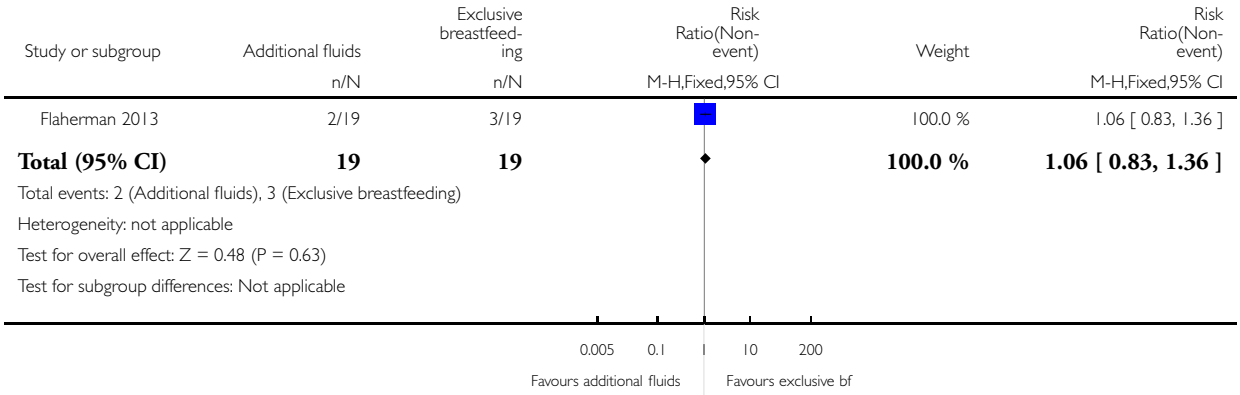


Analysis 1.3. Comparison 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants, Outcome 3 Incidence of fever.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants

Outcome: 3 Incidence of fever

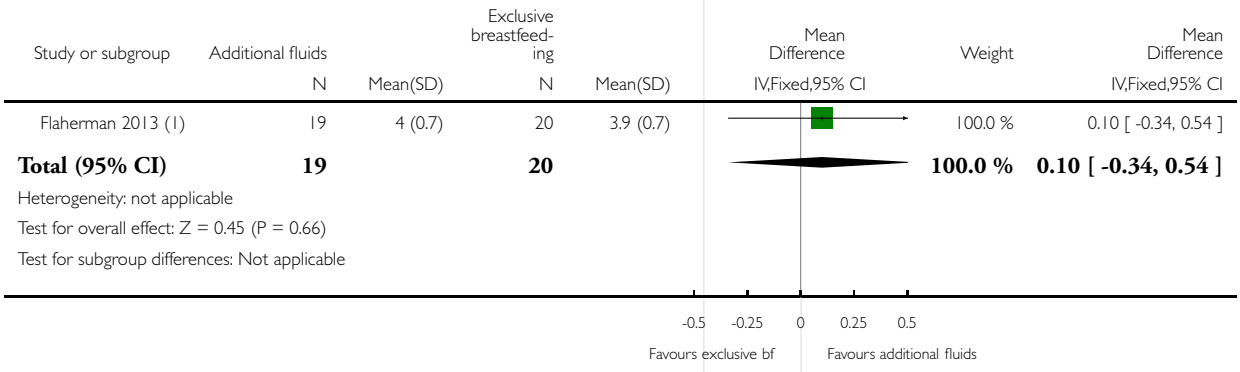


Analysis 1.4. Comparison 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants, Outcome 4 Maternal self-confidence - Modified breastfeeding self-efficacy score at 1 week.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants

Outcome: 4 Maternal self-confidence - Modified breastfeeding self-efficacy score at 1 week



(1) Items rated on a scale from 1 (" Strongly Disagree") to 5 (" Strongly Agree"), with higher scores associated with increased breastfeeding self-efficacy.

Analysis 1.5. Comparison 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants, Outcome 5 Phototherapy in hospital or home.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 1 Non-exclusive breastfeeding infants (artificial milk) versus exclusive breastfeeding infants

Outcome: 5 Phototherapy in hospital or home

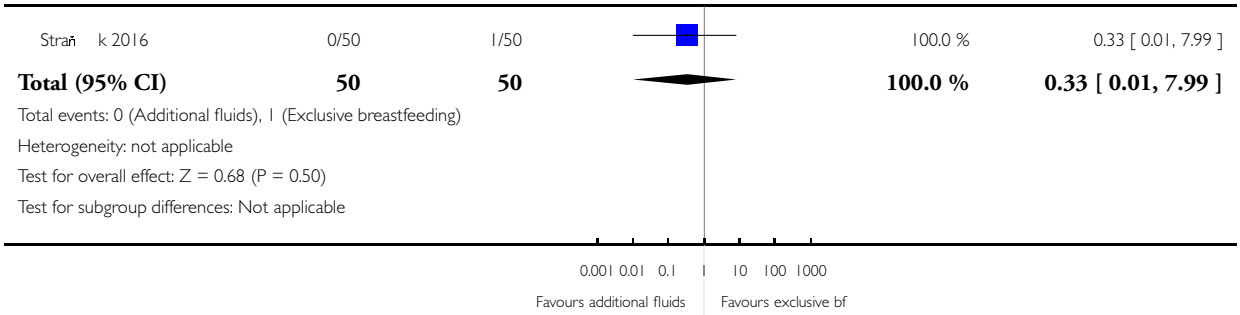
Study or subgroup	Additional fluids n/N	Exclusive breastfeeding n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Straň k 2016	0/50	1/50		100.0 %	0.33 [0.01, 7.99]
Total (95% CI)	**50**	**50**		**100.0 %**	**0.33 [0.01, 7.99]**

Total events: 0 (Additional fluids), 1 (Exclusive breastfeeding)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 1 Breastfeeding duration.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 1 Breastfeeding duration

Study or subgroup	Additional fluids n/N	Exclusive breastfeeding n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Any breastfeeding at 4 weeks					
Martin-Calama 1997	64/83	81/87		100.0 %	0.83 [0.73, 0.94]
Subtotal (95% CI)	**83**	**87**		**100.0 %**	**0.83 [0.73, 0.94]**
Total events: 64 (Additional fluids), 81 (Exclusive breastfeeding)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.83 (P = 0.0046)					
2 Any breastfeeding at 8 weeks					
Martin-Calama 1997	53/83	70/87		100.0 %	0.79 [0.65, 0.96]
Subtotal (95% CI)	**83**	**87**		**100.0 %**	**0.79 [0.65, 0.96]**
Total events: 53 (Additional fluids), 70 (Exclusive breastfeeding)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
3 Any breastfeeding at 12 weeks					
Martin-Calama 1997	42/83	65/87		100.0 %	0.68 [0.53, 0.87]
Subtotal (95% CI)	**83**	**87**		**100.0 %**	**0.68 [0.53, 0.87]**
Total events: 42 (Additional fluids), 65 (Exclusive breastfeeding)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0018)					
4 Any breastfeeding at 16 weeks					
Martin-Calama 1997	36/83	58/87		100.0 %	0.65 [0.49, 0.87]
Subtotal (95% CI)	**83**	**87**		**100.0 %**	**0.65 [0.49, 0.87]**
Total events: 36 (Additional fluids), 58 (Exclusive breastfeeding)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.93 (P = 0.0034)					
5 Any breastfeeding at 20 weeks					
Martin-Calama 1997	33/83	50/87		100.0 %	0.69 [0.50, 0.95]
Subtotal (95% CI)	**83**	**87**		**100.0 %**	**0.69 [0.50, 0.95]**
Total events: 33 (Additional fluids), 50 (Exclusive breastfeeding)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.25 (P = 0.024)					

Analysis 2.2. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 2 Maximum temperature (°C).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 2 Maximum temperature (C)

Study or subgroup	Additional fluids		Exclusive breastfeeding		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 At 72 hours							
Martin-Calama 1997	83	37.3 (0.3)	87	37.4 (0.3)		100.0 %	-0.10 [-0.19, -0.01]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**-0.10 [-0.19, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.17 (P = 0.030)							

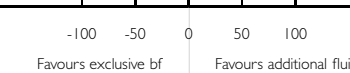
Analysis 2.3. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 3 Minimum temperature (°C).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 3 Minimum temperature (C)

Study or subgroup	Additional fluids		Exclusive breastfeeding		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 At 72 hours							
Martin-Calama 1997	83	36.5 (0.2)	87	36.6 (0.3)		100.0 %	-0.10 [-0.18, -0.02]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**-0.10 [-0.18, -0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.57 (P = 0.010)							

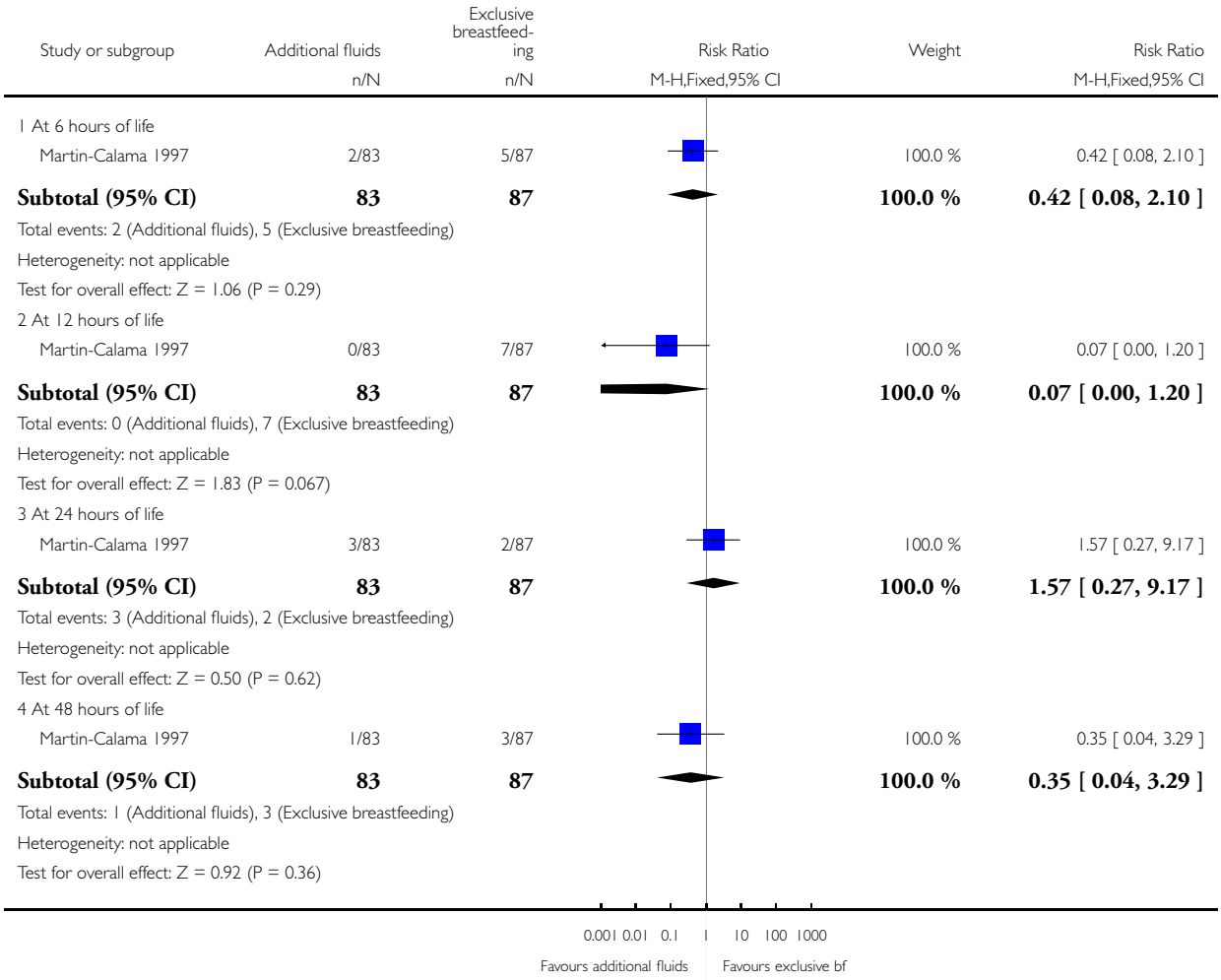


Analysis 2.4. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 4 Episodes of hypoglycaemia (glycaemia < 2.2 mmol/L).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 4 Episodes of hypoglycaemia (glycaemia < 2.2 mmol/L)



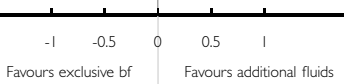
Analysis 2.5. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 5 Mean capillary blood glucose levels of infants (mmol/L).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 5 Mean capillary blood glucose levels of infants (mmol/L)

Study or subgroup	Additional fluids		Exclusive breastfeeding		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 At 6 hours of life							
Martin-Calama 1997	83	3.68 (0.93)	87	3.39 (0.89)		100.0 %	0.29 [0.02, 0.56]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**0.29 [0.02, 0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.08 (P = 0.038)							
2 At 12 hours of life							
Martin-Calama 1997	83	3.73 (0.77)	87	3.26 (0.78)		100.0 %	0.47 [0.24, 0.70]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**0.47 [0.24, 0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.95 (P = 0.000077)							
3 At 24 hours of life							
Martin-Calama 1997	83	3.73 (0.91)	87	3.39 (0.78)		100.0 %	0.34 [0.08, 0.60]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**0.34 [0.08, 0.60]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.61 (P = 0.0091)							
4 At 48 hours of life							
Martin-Calama 1997	83	3.78 (0.92)	87	3.54 (0.84)		100.0 %	0.24 [-0.03, 0.51]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**0.24 [-0.03, 0.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.77 (P = 0.076)							



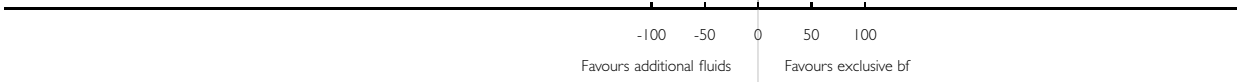
Analysis 2.6. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 6 Weight change (loss) (g).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 6 Weight change (loss) (g)

Study or subgroup	Favours additional fluids N	Mean(SD)	Exclusive breastfeeding N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 6 hours of life							
Martin-Calama 1997	83	39.4 (22.2)	87	46.4 (19.1)		100.0 %	-7.00 [-13.24, -0.76]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**-7.00 [-13.24, -0.76]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.20 (P = 0.028)							
2 At 12 hours of life							
Martin-Calama 1997	83	74.9 (34.5)	87	86.4 (30.4)		100.0 %	-11.50 [-21.29, -1.71]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**-11.50 [-21.29, -1.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.30 (P = 0.021)							
3 At 24 hours of life							
Martin-Calama 1997	83	127.2 (43.8)	87	140.6 (42.4)		100.0 %	-13.40 [-26.37, -0.43]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**-13.40 [-26.37, -0.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.03 (P = 0.043)							
4 At 48 hours of life							
Martin-Calama 1997	83	165.3 (56.4)	87	197.8 (73.2)		100.0 %	-32.50 [-52.09, -12.91]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**-32.50 [-52.09, -12.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.25 (P = 0.0011)							
5 At 72 hours of life							
Martin-Calama 1997	83	144.9 (68.5)	87	141.9 (89.1)		100.0 %	3.00 [-20.83, 26.83]
Subtotal (95% CI)	**83**		**87**			**100.0 %**	**3.00 [-20.83, 26.83]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.25 (P = 0.81)							



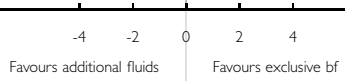
Analysis 2.7. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 7 Weight loss (%).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 7 Weight loss (%)

Study or subgroup	Additional fluids N	Mean(SD)	Exclusive breastfeeding N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Day 3							
Nicoll 1982 (1)	33	4.97 (1.8)	14	6 (2)		100.0 %	-1.03 [-2.24, 0.18]
Subtotal (95% CI)	**33**		**14**			**100.0 %**	**-1.03 [-2.24, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.66 (P = 0.096)							
2 Day 5							
Nicoll 1982	33	4.1 (1.7)	14	4.3 (0.6)		100.0 %	-0.20 [-0.86, 0.46]
Subtotal (95% CI)	**33**		**14**			**100.0 %**	**-0.20 [-0.86, 0.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.59 (P = 0.55)							



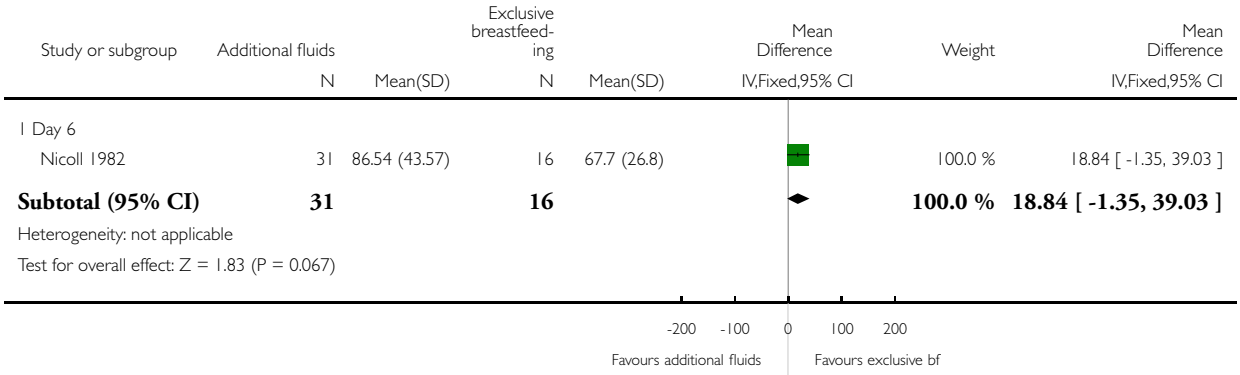
(1) Loss as percentage of baby's birthweight. Data for separate glucose and water arms have been combined.

Analysis 2.8. Comparison 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants, Outcome 8 Maximum serum bilirubin levels umol/L.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 2 Non-exclusive breastfeeding infants (water) versus exclusive breastfeeding infants

Outcome: 8 Maximum serum bilirubin levels umol/L

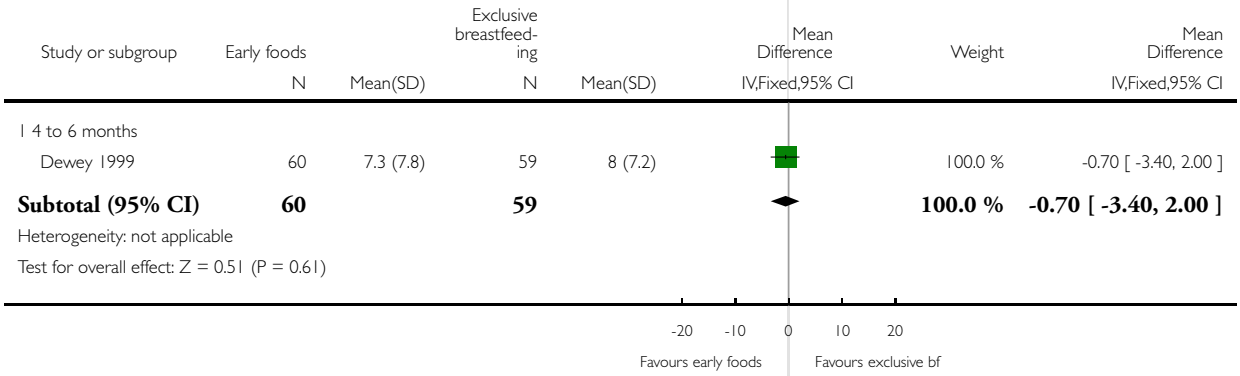


Analysis 3.1. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 1 Fever (% of days).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 1 Fever (% of days)

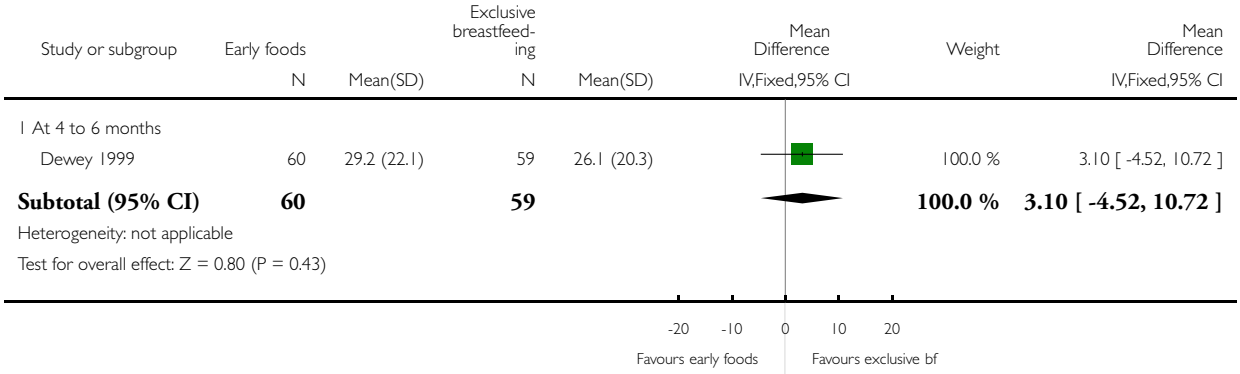


Analysis 3.2. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 2 Cough (% of days).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 2 Cough (% of days)

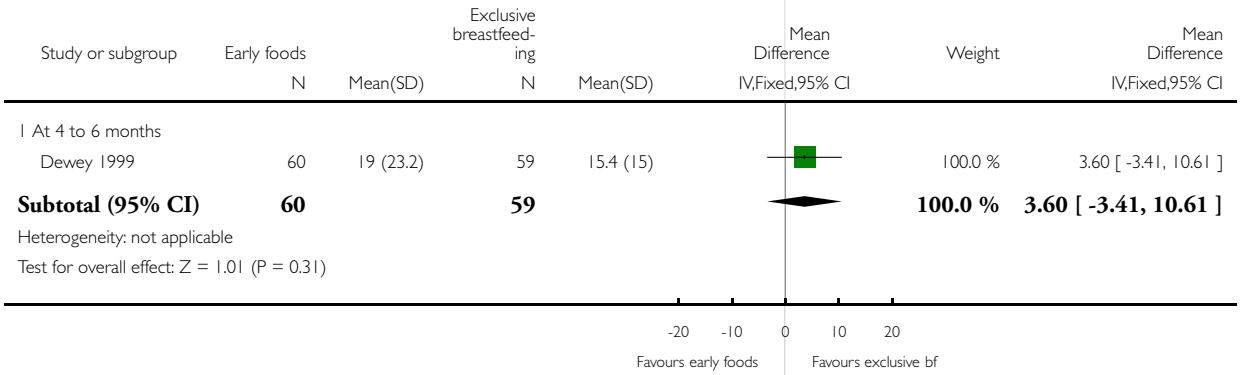


Analysis 3.3. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 3 Congestion (% of days).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 3 Congestion (% of days)



Analysis 3.4. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 4 Nasal discharge (% of days).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 4 Nasal discharge (% of days)

Study or subgroup	Early foods N	Mean(SD)	Exclusive breastfeeding N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 4 to 6 months							
Dewey 1999	60	16.2 (17.1)	59	12 (12.2)		100.0 %	4.20 [-1.13, 9.53]
Subtotal (95% CI)	**60**		**59**			**100.0 %**	**4.20 [-1.13, 9.53]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.54 (P = 0.12)							

Analysis 3.5. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 5 Hoarseness (% of days).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 5 Hoarseness (% of days)

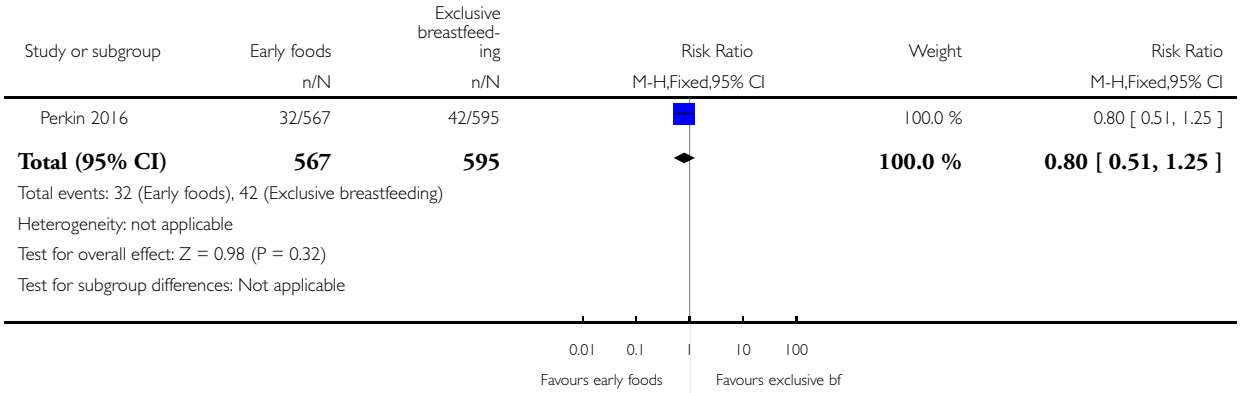
Study or subgroup	Early foods N	Mean(SD)	Exclusive breastfeeding N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 4 to 6 months							
Dewey 1999	60	2.6 (6.3)	59	2.5 (4.3)		100.0 %	0.10 [-1.84, 2.04]
Subtotal (95% CI)	**60**		**59**			**100.0 %**	**0.10 [-1.84, 2.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.10 (P = 0.92)							

Analysis 3.6. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 6 "Food allergy" to one or more foods between 1-3 years of age.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 6 "Food allergy" to one or more foods between 1-3 years of age

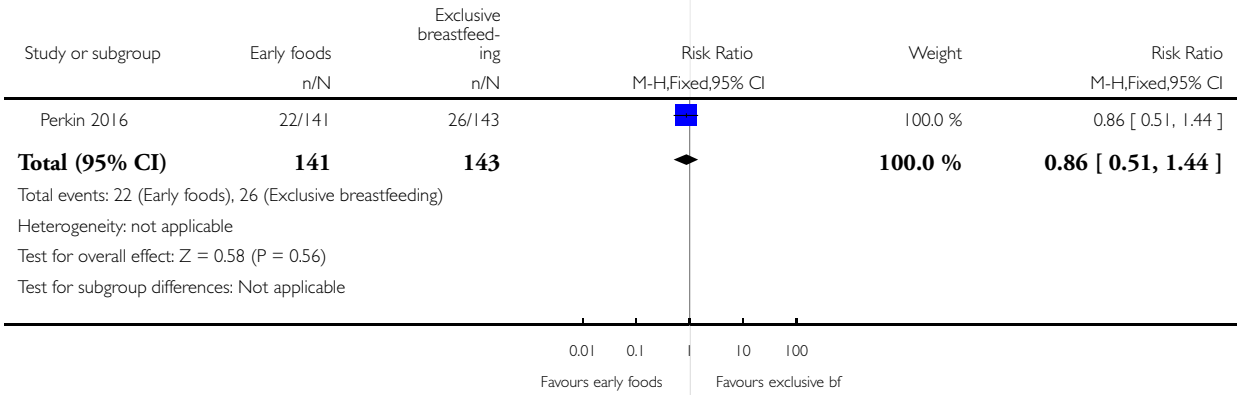


Analysis 3.7. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 7 Visible eczema at 12-month visit stratified by visible eczema at enrolment.

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 7 Visible eczema at 12-month visit stratified by visible eczema at enrolment



Analysis 3.8. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 8 Food protein enterocolitis syndrome positive response to challenge (number of children).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 8 Food protein enterocolitis syndrome positive response to challenge (number of children)

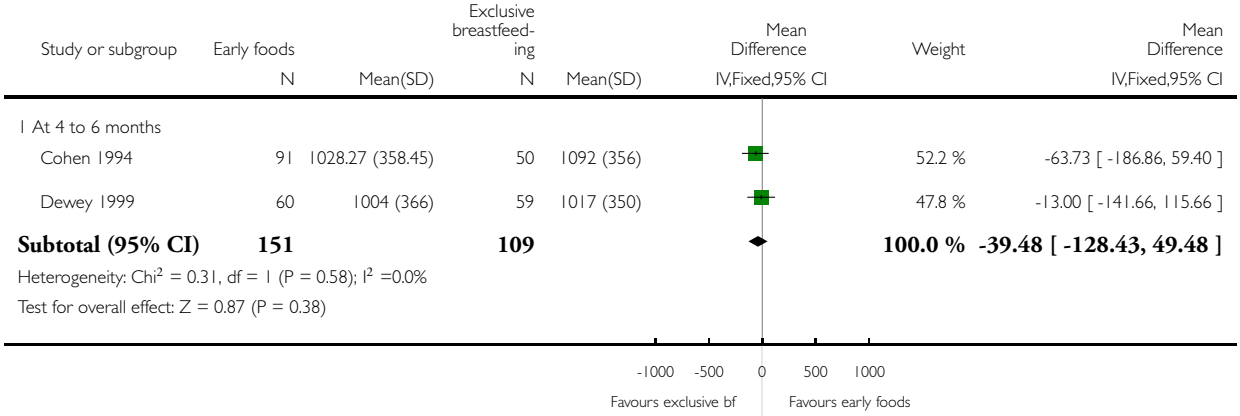
Study or subgroup	Early foods n/N	Exclusive bf n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Perkin 2016	2/651	1/652		100.0 %	2.00 [0.18, 22.04]
Total (95% CI)	**651**	**652**		**100.0 %**	**2.00 [0.18, 22.04]**
Total events: 2 (Early foods), 1 (Exclusive bf)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					

Analysis 3.9. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 9 Weight change (gain) (g).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 9 Weight change (gain) (g)

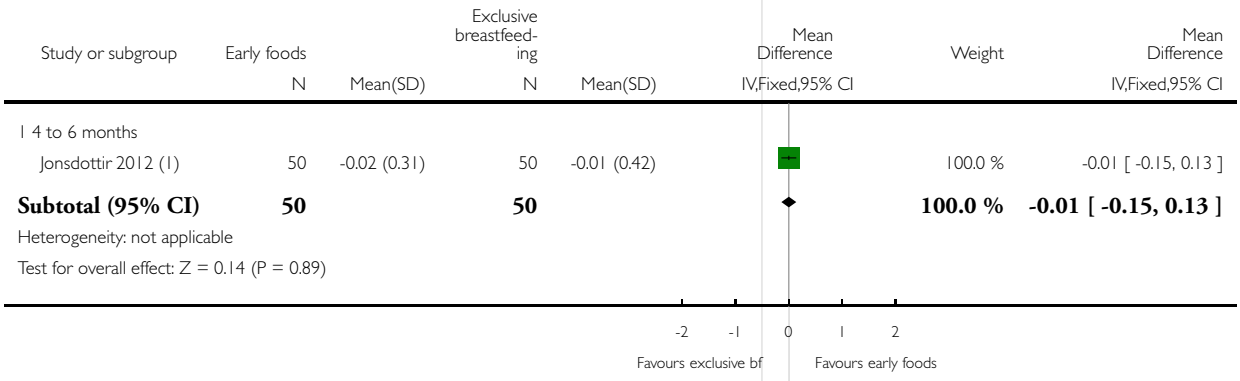


Analysis 3.10. Comparison 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants, Outcome 10 Weight change (z score).

Review: Early additional food and fluids for healthy breastfed full-term infants

Comparison: 3 Non-exclusive breastfeeding infants (foods) versus exclusive breastfeeding infants

Outcome: 10 Weight change (z score)



(1) Data estimated from graph. Trialists changed weights to z scores using World HealthOrganization (WHO) standards.

ADDITIONAL TABLES

Table 1. Martin-Calama 1997. Primary outcome: breastfeeding duration

% of mothers who continued either exclusive or partial breastfeeding	Exclusive breastfeeding on day 1-3 group (non-glucose water) (n = 87)	Glucose water on day 1-3 (n = 83)
At 4 weeks	93%	77%
At 8 weeks	81%	64%
At 12 weeks	75%	51%
At 16 weeks	67%	43%
At 20 weeks	57%	40%

These figures were estimated from a graph (Figure 2) on page 212 of the Martin-Calama 1997 paper.

WHAT'S NEW

Date	Event	Description
1 March 2016	New citation required but conclusions have not changed	Conclusions unchanged.
1 March 2016	New search has been performed	Search updated and two additional trials (Lindfors 1988; Straňák 2016) included. One trial previously listed as ongoing, now published, has also been included (Perkin 2016). Two new ongoing trials were identified (Flaherman 2014; Kair 2014). Seven more studies have been added to 'Excluded studies' (Cameron 2015; de Jong 1998; Du Toit 2015; Juvonen 1996; Kimani-Murage 2013; Flaherman 2011; Saarinen 1999). Three 'Summary of findings' tables have been incorporated in this update

HISTORY

Date	Event	Description
28 March 2014	New citation required but conclusions have not changed	There have been no major changes made to the conclusions of the review since the last update
28 March 2014	New search has been performed	Two additional trials have been included (Flaherman 2013; Jonsdottir 2012). One additional paper to an already included trial has also been added (Cohen 1994). Six more studies have been added to 'Excluded studies' (de Oliveira 2012; French 2012; Krebs 2013; Olaya 2013; Schiess 2010; Ziegler 2011).

CONTRIBUTIONS OF AUTHORS

Previous version of the review

Genevieve Becker co-ordinated the review update. Genevieve Becker and Tracey Remmington assessed study eligibility independently extracted data and entered data. Genevieve Becker wrote the first draft with input from Tracey Remmington (Becker 2014).

Current version of the review

Hazel A Smith co-ordinated the review update. Hazel A Smith and Genevieve Becker assessed study eligibility independently extracted data and entered data. Hazel A Smith lead on the analysis aspects and Genevieve Becker lead on the text; both authors agreed the final draft.

DECLARATIONS OF INTEREST

In October 2012 Hazel A Smith registered as a PhD student to study the effects of infant's milk diet at two months of age on their body composition, growth and neurodevelopment in the first 2 years of life. Hazel is the Research Coordinator for the Paediatric Intensive Care Unit in Our Lady's Children's Hospital, Ireland. Hazel is not in receipt of any financial relationship with any commercial entity.

Genevieve Becker works in the general area of infant and young child feeding but not specifically connected with the topic of this review. Genevieve is not in receipt of any financial relationship with any commercial entity.

SOURCES OF SUPPORT

Internal sources

- G Becker and HA Smith undertook the update of this review as volunteers with no funding or protected time support, Ireland.

External sources

- Cochrane Pregnancy and Childbirth received a grant from the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the Background section and refocused to reflect exclusive breastfeeding as the norm and supplementation as an intervention, as well as more justification for the outcomes selected for examination.

Outcomes as listed in the protocol amended to (primary) physiological jaundice, absence or presence, and if present, duration (days), and (secondary) phototherapy in hospital or home setting if required, absence or presence, and if present, duration (days). This was changed in recognition that some participants are likely not to be jaundiced or to need phototherapy.

In the 2016 update, the outcomes "Weight change" was changed to "Measures of weight, growth and development" so as to include measures such as height, head circumference, and developmental aspects that may be included in trials, and "Maternal self-confidence in breastfeeding" was changed to "Confidence in breastfeeding" in order to include trials that examined confidence of fathers and other family members, health workers or those with significant influence on the mother. Infant morbidity examples were expanded to include hypoglycaemia and symptoms of allergy.

We have updated the methods in accordance with the updated *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In the 2016 update, we have assessed the evidence using the GRADE approach and added 'Summary of findings' tables.

NOTES

In the next update, we will review the outcomes listed for their relevance in the future, and combine/reduce outcomes related to jaundice and hyperbilirubinaemia.

INDEX TERMS

Medical Subject Headings (MeSH)

*Breast Feeding [statistics & numerical data]; *Dietary Supplements [adverse effects]; Dietary Carbohydrates [administration & dosage; adverse effects]; Drinking Water [administration & dosage; adverse effects]; Glucose [administration & dosage]; Infant Food [*adverse effects]; Randomized Controlled Trials as Topic; Term Birth; Time Factors

MeSH check words

Humans; Infant; Infant, Newborn