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Dietary modifications for infantile colic (Review)

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[Intervention Review]

Dietary modifications for infantile colic

Morris Gordon[1], Elena Biagioli[2], Miriam Sorrenti[3], Carla Lingua[4], Lorenzo Moja[5], Shel SC Banks[6], Simone Ceratto[3,7], Francesco Savino[3]

[1]School of Medicine, University of Central Lancashire, Preston, UK. [2]Laboratory Methodology for Clinical Research, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy. [3]Department of Pediatrics, Regina Margherita Children's Hospital, Turin, Italy. [4]Department of Public and Pediatric Health Sciences, University of Turin, Turin, Italy. [5]Department of Biomedical Sciences for Health, University of Milan, Milan, Switzerland. [6]Department of Child Health, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, UK. [7]Department of Sciences of Public Health and Pediatrics, University of Turin, Regina Margherita Children's Hospital, Turin, Italy

Contact address: Francesco Savino, Department of Pediatrics, Regina Margherita Children's Hospital, P.zza Polonia 94, Turin, 10126, Italy. francesco.savino@unito.it.

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ABSTRACT

Background

Infantile colic is typically defined as full-force crying for at least three hours per day, on at least three days per week, for at least three weeks. Colic appears to be more frequent in the first six weeks of life (prevalence range of 17% to 25%), depending on the specific location reported and definitions used, and usually resolves by three months. The aetiopathogenesis of infantile colic is unclear but most likely multifactorial. A number of psychological, behavioural and biological components (food hypersensitivity, allergy or both; gut microflora and dysmotility) are thought to contribute to it. The role of diet as a component in infantile colic remains controversial.

Objectives

To assess the effects of dietary modifications for reducing colic in infants less than four months of age.

Search methods

In July 2018 we searched CENTRAL, MEDLINE, Embase, 17 other databases and 2 trials registers. We also searched Google, checked references and contacted study authors.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs evaluating the effects of dietary modifications, alone or in combination, for colicky infants younger than four months of age versus another intervention or placebo. We used specific definitions for colic, age of onset and the methods for performing the intervention. We defined 'modified diet' as any diet altered to include or exclude certain components.

Data collection and analysis

We used standard Cochrane methodological procedures. Our primary outcome was duration of crying, and secondary outcomes were response to intervention, frequency of crying episodes, parental/family quality of life, infant sleep duration, parental satisfaction and adverse effects.

Main results

We included 15 RCTs involving 1121 infants aged 2 to 16 weeks. All studies were small and at high risk of bias across multiple design factors (e.g. selection, attrition). The studies covered a wide range of dietary interventions, and there was no scope for meta-analysis. Using GRADE, we assessed the quality of the evidence as very low.

No study reported on parental or family quality of life, infant sleep duration per 24 h, or parental satisfaction.

Low-allergen maternal diet versus a diet containing potential allergens: one study (90 infants) found that 35/47 (74%) of infants responded (reduction in cry/fuss duration of 25%) to a low-allergen maternal diet, compared with 16/43 (37%) of infants with a maternal diet containing potential allergens (37% difference; 95% confidence interval (CI) 18 to 56; P < 0.001).

Low-allergen diet or soy milk formula versus standard diet or cow's milk formula and dicyclomine hydrochloride: one study (120 infants) found that 10/15 (66.6%) breastfed babies responded to dicyclomine hydrochloride and a normal diet, compared with 10/16 (62.5%) on a low-allergen diet, while 24/45 (53.3%) standard formula-fed babies taking dicyclomine hydrochloride improved compared with 29/44 (65.9%) on soy milk formula. Response was defined as a reduction of crying to less than one hour per day after 48 hours of treatment, with remission persisting for one month.

Hydrolysed formula versus standard formula: one study (43 infants) reported that the number of infants who responded to the intervention (cried for less than 3 hours per day on at least 3 days a week) was 8/23 in the whey hydrolysate group versus 5/20 in the standard formula group (χ^2 using yate's correction = 0.20, P = 0.65).

The same study (43 infants) reported a greater reduction in crying time postintervention with hydrolysed formula (104 min/d, 95% CI 55 to 155) than with standard formula (3 min/d, 95% CI −63 to 67); difference = 101 min/d, 95% CI 25 to 179; P = 0.02).

The author confirmed there were no adverse effects.

Hydrolysed formula or dairy- and soy-free maternal diet versus standard diet/formula and parental education or counselling: one study (21 infants) found that crying time decreased to 2.03 h/d (SD 1.03) in the hydrolysed or dairy- and soy-free maternal diet group compared with 1.08 h/d (SD 0.7) in the parent education or counselling group, nine days postintervention.

Partially hydrolysed, lower lactose, whey-based formulae containing oligosaccharide versus standard formula with simethicone: one study (267 infants) found both groups experienced decreased colic episodes after seven days (partially hydrolysed formula: from 5.99 episodes (SD 1.84) to 2.47 episodes (SD 1.94); standard formula: from 5.41 episodes (SD 1.88) to 3.72 episodes (SD 1.98)); 95% CI 95% −0.7 to −1.8; P < 0.001). This difference was significant after two weeks (partially hydrolysed: 1.76 episodes (SD 1.60); standard formula: 3.32 episodes (SD 2.06); P < 0.001). The study author confirmed there were no adverse effects.

Lactase enzyme supplementation versus placebo: three studies (138 infants) assessed this comparison, but they are cross-over trials that did not report data from before washout. There were no adverse effects in any of the studies.

Extract of *Foeniculum vulgare, Matricariae recutita*, and *Melissa officinalis* versus placebo: one study (93 infants) found that average daily crying time was lower for infants given the extract (76.9 min/d (SD 23.5), than infants given placebo (169.9 min/d (SD 23.1) at the end of the one-week study (95% CI −102.89 to −83.11; P < 0.01). There were no adverse effects.

Soy protein-based formula versus standard cows' milk protein-based formula: one study (19 infants) reported a mean crying time of 12.7 h/week (SD 16.4) in the soy formula group versus 17.3 h/week (SD 6.9) in the standard cows' milk group, and that 5/10 (50%) responded in the soy formula group versus 0/9 (0%) in the standard cows' milk group.

Soy protein formula with polysaccharide versus standard soy protein formula: one cross-over study (27 infants) assessed this comparison but did not provide disaggregated data for the pre-wash-out data.

Authors' conclusions

Currently, evidence of the effectiveness of dietary modifications for the treatment of infantile colic is sparse and at significant risk of bias. The few available studies had small sample sizes, and most had serious limitations. There were insufficient studies, making the use of meta-analysis unfeasable. Benefits reported for hydrolysed formulas were inconsistent.

Based on available evidence, we are unable to recommend any intervention. Future studies of single interventions, using clinically significant outcome measures, and appropriate design and power are needed.

PLAIN LANGUAGE SUMMARY

Diet changes for infant colic

Review question

Do colicky infants show an improvement when breastfeeding mothers follow a low-allergen diet, or when formula-fed infants are fed a special formula?

Background

Infantile colic is a common problem afflicting otherwise healthy infants in the first three months of life. It is characterised by episodes of inconsolable crying lasting for longer than three hours per day, for more than three days a week, for at least three weeks.

It can be very distressing for parents.

Dietary changes, such as removing cows' milk from a breastfeeding mother's diet or switching formula-fed babies to a special soy-based formula, might reduce the symptoms of colic.

Study characteristics

We found 15 randomised controlled trials, a type of study in which participants are randomly assigned to one of two or more treatment groups, involving a total of 1121 babies with colic. The evidence is current to July 2018.

Infants (balanced between boys and girls) were less than three months of age.

Key results

Most studies reported data on a combination of outcomes: duration of crying, number of responders in each group after treatment (i.e. those who experienced a decrease in daily crying), or frequency of crying episodes. We present these findings below. No study reported on parental or family quality of life, infant sleep or parental satisfaction. Six studies reported that there were no side effects as a result of the dietary changes.

Low-allergen diet

One study (90 infants) found that more breastfed infants responded to a low-allergen maternal diet than infants on a standard diet containing known potential allergens.

Another study (120 infants) found little difference in breastfed infants whose mothers were given a low-allergen diet (10/16, 62.5%) and formula-fed babies who were given soy milk (29/44, 65.9%), but the researchers did find that breastfed babies responded more to dicyclomine hydrochloride (a tablet for treating stomach spasms) than formula-fed babies.

Hydrolysed formula milk

One study (43 infants) found no clear difference in resolving symptoms of colic between the hydrolysed (hypoallergenic) and standard cow's milk groups. They also reported a greater reduction in crying time at study end in infants who were given hydrolysed, and reported no adverse effects.

A third study (21 infants) reported that infants whose parents were given information and support experienced a more rapid reduction in crying time than infants who were given a hydrolysed formula or dairy- and soy-free diet (within nine days).

A fourth study (267 infants) found that both partially hydrolysed formula with oligosaccharides (carbohydrates) and a standard formula with simethicone (a drug for treating symptoms of gas) reduced colic episodes after seven days, but effects were greater in the hydrolysed plus oligosaccharides group after two weeks. The study author confirmed there were no adverse effects.

Lactase enzyme supplementation

Three studies (138 infants) tested the effect of adding lactase (an enzyme which helps break down the lactose (sugar) in milk) to the infants' milk. There were no adverse effects in any of the studies.

Fennel, chamomile and lemon balm extract

One study (93 infants) found that average daily crying time in breastfed babies reduced within one week of treatment with a fennel, chamomile and lemon balm extract. There were no adverse effects.

Soy protein-based formula

One study (19 infants) found that, compared with cows' milk formula, soy formula reduced crying time and increased the number of responders. However, international guidance does not support the use of soy milk due to concerns that they can impact hormones in babies, so these results are not relevant.

Quality of the evidence

Many of the studies included only small numbers of participants and were of poor quality. We did not find evidence of effectiveness for most dietary interventions. Where studies did report some benefit, this was not large enough to be meaningful.

Conclusions

Based on the available evidence, we are not able to recommend any of the dietary modifications assessed in this review.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: dietary interventions for infantile colic versus placebo or other interventions

Dietary interventions for infantile colic versus placebo or other interventions

Patient or population: infants with colic defined by recognised criteria

Settings: outpatient

Intervention: any dietary intervention to treat infantile colic

Comparison: placebo or any other intervention

Outcomes	Impacts	Number of studies[a]	Quality of the evidence (GRADE)
Duration of crying	This was the most commonly reported outcome, but studies did so in an extremely heterogenous manner due to measurement tools used, as well as time and frequency of determination. There was no clear effect as regards the efficacy of any of the agents under study for reducing the duration of crying in affected infants. One study reported that the number of infants crying for less than 3 hours per day on at least 3 days a week following the intervention was 8 (out of 23) in the whey hydrolysate group versus 5 (out of 20) in the standard formula group ($\chi^2 = 0.20$, P = 0.65). Results from 3 individual studies found that a hydrolysed formula, herbal drops and soy protein-based formula may reduce crying time at study end (continuous outcome). 1 study found no difference between 2 types of hydrolysed formulas.	6	⊕⊖⊖⊖ **Very low[b]**
Number of responders in each group after treatment	There were mixed effects as regards the efficacy of the agents under study for improving the number of responders. Results from 2 individual studies showed that a low-allergen maternal diet and a soy protein-based formula may increase the number of responders. However, another study found no evidence in favour of a low-allergen diet or soy-milk formula but did find that dicyclomine hydrochloride may increase the number of breastfed babies who respond.	3	⊕⊖⊖⊖ **Very low[b]**
Frequency of crying episodes per 24 h	Results from 2 individual studies showed that a hydrolysed or dairy- and soy-free formula and a partially hydrolysed formula may reduce the frequency of crying episodes per 24 h. As this is very difficult to discern from normality and is not a key component of infantile colic diagnostic criteria or a necessary a goal of clinicians, the clinical relevance of this outcome is worth readers' consideration.	2	⊕⊖⊖⊖ **Very low[b]**
Parental or family quality of life, including measures of parental stress, anxiety or depression	No data		

Infant sleep duration per 24 h at 7, 14 and 21 days from start of intervention	No data		
Parental satisfaction	No data		
Adverse effects to dietary modifications	This is a key outcome, given the population under study, which was poorly reported in many studies. 3 studies reported that there were no adverse effects. 3 authors (one of whom is an author on this review) of 3 other studies confirmed there were no adverse effects. The 9 remaining studies did not report on adverse effects.	6	⊕⊖⊖⊖ **Very low**[b]

GRADE Working Group – grades of evidence

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

[a]Participant numbers have not been included in the table as it contains multiple comparisons.
[b]We downgraded the quality of the evidence for all outcomes, across all studies, due to consistent issues with incomplete outcome data, selective reporting, the presence of extremely small sample sizes, drug and nutrition company involvement, and risk of bias. These issues were pervasive across the evidence base and must be considered when interpreting any of the reported findings.

BACKGROUND

The most frequently cited definition of infantile colic is the rule of three: unexplained episodes of paroxysmal crying for longer than three hours per day, for three days per week, for at least three weeks (Wessel 1954). More recently, colic has been included under functional gastrointestinal disorders (Rome IV diagnostic criteria), and the definition has been expanded to include paroxysms of irritability and fussiness for at least one week in an infant that has no failure to thrive (Drossman 2016).

This condition appears to be more frequent in the first six weeks of life, occurring in 17% to 25% of newborns, depending on geography and definitions employed, with prevalence often peaking at that point. It is important to note that without any intervention, colic symptoms are usually below the threshold of such diagnostic criteria by three months of age (Reijneveld 2001; Vandenplas 2015; Wolke 2017).

Description of the condition

Paroxysms of inconsolable crying due to colic are often accompanied by flushing of the face, meteorism (excessive flatulence in the intestinal tract with distention of the abdomen), drawing-up of the legs, and flatulence (Gupta 2007; Savino 2010). Symptoms typically start in the second week of life in both breastfed and formula-fed infants and usually resolve by three months of age (Lucas 1998; Vandenplas 2017). Generally speaking, these symptoms are not indicative of disease and thus hospital admission for these infants is generally unnecessary, detrimental and not to be encouraged (Savino 2007). However, most understanding of the condition is based on research that includes a cohort of children whose parents have chosen to seek help, so it is worth noting that this may not reflect the whole population, and what separates colic from non-colic may simply be the parents' decision to self-seek care (further discussions on this point are outside of the scope of this review). Furthermore, five per cent of colicky crying infants do have a serious underlying medical problem (Freedman 2009; Savino 2005; Savino 2007). Thus, clinicians should assess all colicky infants to rule out underlying medical conditions that require investigation and treatment (Savino 2010).

The aetiopathogenesis of infantile colic remains undefined and is most likely multifactorial. Despite the common nature of the condition, there is a general paucity of evidence investigating this area. Different authors have suggested that a number of behavioural (psychological and social) and biological (food hypersensitivity or allergy (or both) components (Clifford 2002); gut microflora and dysmotility) factors can contribute to its manifestation (Camilleri 2017). These include the following.

First, lactose intolerance – due to a relative lactase deficiency – has been postulated as a possible causative factor in infant colic. Carbohydrate malabsorption leads to colonic fermentation of sugars and an increase in levels of hydrogen gas. The rapid production of hydrogen in the lower bowel distends the colon, sometimes causing pain, whereas the osmotic pressures generated by lactose and lactic acid in the colon cause an influx of water, leading to further distension of the bowel. Although studies evaluating the degree of hydrogen in the breath of colicky infants have produced inconsistent results, some studies have reported increases in breath hydrogen levels (Hyams 1989; Miller 1990; Moore 1988).

Second, the immunological model of colic focuses on possible allergens, such as cows' milk proteins in breast milk or infant formula, as the cause of colic. Intact proteins from the mother's diet are hypothesised to cross over into the breast milk and provoke an allergic response and symptoms of colic in some infants. Consequently, some authors have proposed a low-allergen maternal diet as a form of treatment (Hill 2005; Schach 2002). Shannon 1921 was the first to raise the possibility that infantile colic could be related to allergens. Since then, a number of studies have evaluated the possible association between colic and food hypersensitivity (Campbell 1989; Estep 2000; Forsyth 1989; Hill 1995; Hill 2005; Iacono 1991; Jakobsson 1983; Lindberg 1999; Lothe 1987; Lucassen 2000). Articles in favour of this hypothesis report that about 25% of infants with moderate or severe symptoms might have cows' milk protein-dependent colic (Axelsson 1986; Hill 2000; Lindberg 1999), which improves after some days of a hypoallergenic diet (Campbell 1989; Dupont 2010; Estep 2000; Iacono 1991; Iacono 2005; Jakobsson 1983; Jakobsson 2000; Savino 2001). For these infants, infantile colic has been identified as the first possible manifestation of atopic disease, and dietetic treatment should be the first therapeutic approach (Gupta 2007; Hall 2012; Perry 2011; Savino 2010). Indeed, dietary changes, such as eliminating cows' milk proteins, are particularly indicated in cases of suspected intolerance to cows' milk proteins (for example, in infants with a positive family history; atopic disease such as asthma, eczema and other immune disorders; onset after the first month of life; and colic associated with other gastrointestinal symptoms such as reflux, vomiting or diarrhoea) (Hill 1995; Hill 2005; Jakobsson 1983; Lucassen 2000).

Third, there is growing evidence that intestinal microbiota in colicky infants differ from those in healthy controls; research has shown higher levels of anaerobic bacteria, such as coliform and *Escherichia coli*, and a lower concentration of lactobacilli, in infants with colic (Savino 2010).

Advances in molecular technologies utilising 16S ribosomal RNA and ribosomal DNA created the opportunity for researchers to index the intestinal microbial composition to better understand its association with infantile colic. The researchers found that infants who manifested symptoms of colic were colonised with significantly higher levels of Proteobacteria and exhibited lower bacterial diversity when compared to their unaffected counterparts (Dubois 2016). Additionally, colonisation levels of Actinobacteria *Bifidobacterium* and Firmicute lactobacilli were inversely related to the amount of crying and fussiness in newborns. (de Weerth 2013).

A comparison of formula-fed infants with and without colic revealed significant differences in total bacteria, Enterobacteriaceae and faecal ammonia (Savino 2017).

Human milk naturally contains these prebiotics, defined as indigestible oligosaccharides, which could selectively enhance the proliferation of certain probiotic bacteria in the colon, especially *Bifidobacterium* spp (Thomas 2010). Some studies have failed to find a protective effect of breastfeeding on the development of colic in breastfed infants (Clifford 2002). However, it is unclear whether these studies compared infants who were exclusively breastfed from birth versus infants who were exclusively formula-fed from birth, so it is still unclear whether breastfeeding has

some protective effect or whether artificial feeding compromises the infant gut microbiome in some way. Oligosaccharide prebiotics (a mixture of oligosaccharides (0.8 g/100 mL), comprising 90% galacto-oligosaccharides and 10% fructo-oligosaccharides), may be effective treatments for crying in formula-fed infants with colic (Savino 2006; Vandenplas 2017; Vivatvakin 2010).

More recently, researchers exploring hypotheses and rationale for causes of infantile colic have proposed three hypothetical mechanisms that could potentially be involved in the aetiopathogenesis of infantile colic: immaturity of bile acid mechanisms that alter intraluminal and absorptive mechanisms, immaturity in motility, and alterations in the microbiome (Camilleri 2017).

Description of the intervention

Dietary modifications have often been suggested for both breastfed and formula-fed infants with colic. We examined the following dietary interventions.

Dietary modifications for breastfed, colicky infants who are allergic to certain foods (cows' milk, wheat, eggs, soy, nuts, fish) involve modifying the mother's diet to exclude these components so the infant receives a low-allergen maternal diet. A number of studies have demonstrated a reduction in colic when breastfeeding mothers consumed a hypoallergenic diet (Axelsson 1986; Clyne 1991; Jakobsson 1983; Lothe 1990). For example, Hill 2005 demonstrated that a monitored, low-allergen maternal diet, which excludes cows' milk, eggs, peanuts, tree nuts, wheat, soy and fish, leads to a reduction in distressed behaviour. Estep 2000 also proposed a brief interruption of breastfeeding and a temporary substitution with an amino-acid-based formula; however, this intervention could have negative effects on maternal-infant interaction and on the longer term continuation of breastfeeding and should only ever be considered as a last resort (Savino 2001; Savino 2007; Savino 2010).

For formula-fed infants with colicky symptoms, dietary modifications involve decreasing or removing the intake of cows' milk from the infant's diet, or changing the type of milk formula from starting formulas to special formulas (hypoallergenic formula, soy milk formula, whey hydrolysed formula, casein hydrolysed formula, amino-acid based formula, partially hydrolysed formula, low-lactose milk formula, formula with prebiotic, etc). Some trials have used formulas containing partially hydrolysed whey proteins, low amounts of lactose, prebiotic oligosaccharides, and a high beta palmitic acid content (Oggero 1994; Osborn 2013; Savino 2005; Savino 2006). In formula-fed babies, where an underlying allergy to cows' milk protein is hypothesised to affect the infant, extensively hydrolysed formulas, based on casein or whey, have been shown to reduce colic symptoms (Cohen-Silver 2009; Forsyth 1989; Gupta 2007; Jakobsson 2000; Lucassen 2000). Other studies, hypothesising that malabsorption of lactose may lead to fussing and crying, have tested infant formulas with low-lactose content on the basis that this may reduce excess intestinal gas (Hyams 1989; Infante 2011; Moore 1988; Savino 2003).

Soy formulas may also reduce symptoms of colic in some formula-fed infants. However, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition stated recently that there is no evidence to support the use of soy formulas for managing colic. Additionally, due to concerns regarding a cross-over allergy to cows' milk protein and their oestrogen content, such formulas should not be given to infants with a food allergy during the first six months of life (Agostoni 2006). As far back as 2004, the UK Chief Medical Officer advised against administering soy protein formula to infants under 12 months of age.

Given the clinical and methodological heterogeneity of studies on these interventions, the efficacy of these interventions in reducing infant colic remains inconclusive at present.

How the intervention might work

Managing gut-related symptoms in infants can be challenging. Many factors need to be taken into consideration, including geographical, psychological, behavioural, social and family environments, as well as the dietary approach taken to relieve symptoms of infantile colic.

Many published studies have investigated dietary interventions for reducing colic (Campbell 1989; Clifford 2002; Clyne 1991), proposing a link between infant crying and the gastrointestinal tract, thereby implicating the role of nutritional factors such as lactose, lipids and cows' milk proteins (Feinle-Bisset 2013; Jakobsson 1983; Jakobsson 2000; Lindberg 1999). Cows' milk whey protein elicits symptoms of infantile colic in colicky, formula-fed infants (Lothe 1989). Intact proteins from the mother's diet are hypothesised to cross over into the breast milk and provoke an allergic response and symptoms of colic in some infants (Axelsson 1986; Clyne 1991).

There are several potential pathophysiological mechanisms which could constitute a rational basis for the therapeutic use of dietary interventions, including immunomodulatory and anti-inflammatory actions, and effects on motility and pain perception (Drossman 2016; Gupta 2007; Hill 2000).

Different studies have proposed a possible role of nutrients in the development of infantile colic; Nocerino 2012 investigated potentially harmful metabolites, and Iacovou 2018 suggested that a maternal low FODMAP (fermentable oligo-, di- and mono-saccharides and polyols) diet may be associated with a reduction of infant colic symptoms.

When exploring the causes of colic, we have to consider the possibility that immaturity in hepatic synthesis, reduced levels of intraluminal bile acids and impaired ileal bile absorption of bile acids result in malabsorption of fat and other nutrients. Alternatively, the colonic flora may be abnormal, thereby resulting in increased nutrient fermentations with harmful metabolites, or immaturity of the enteric nervous system might lead to abnormal motility and sensory functions of the intestine and colon (Camilleri 2017).

The growing body of evidence of gut dysfunction support the possible role of nutrients and gut microbiota in the development of infantile colic due to hypersensitivity and abnormal motility (Gupta 2007; Heine 2008; Nocerino 2012). However, the exact mechanisms by which cows' milk and other food allergens induce gastrointestinal motility disorders need further investigation to understand the relationships of these symptoms to the diet (Camilleri 2017; Farré 2013; Heine 2006). Additional factors that could be at play include oversensitivity to stimuli, which may

predispose some infants to irritability, fussing and increased crying (Farré 2013; Keefe 1998; Savino 2007).

It is important to note that when all other pathologies have been ruled out, the natural course of infantile colic is resolution; no intervention is necessary. However, parents are often extremely affected in a variety of ways by the symptoms of colic and seek interventions from multiple sources. This review is clearly situated within the context of utility for such families. Indeed, parents of infants with symptoms of colic who do not seek attention would not be recruited for the studies likely to be found in any review of treatments for infantile colic.

Why it is important to do this review

A number of studies and reviews of the evidence suggest that dietary interventions may be effective in reducing the symptoms of colic in both breastfed and formula-fed infants (Cohen-Silver 2009; Garrison 2000; Hall 2012; Lucassen 2001; Perry 2011; Savino 2010). Potential interventions have included a low-allergen diet for mothers of breastfed infants (Hill 2005), hydrolysed formulas (Forsyth 1989; Jakobsson 2000; Lucassen 2000), or low-lactose content formulas for formula-fed infants (Infante 2011; Savino 2003; Savino 2006). This systematic review examined the effectiveness and safety of dietary modifications for infantile colic, where possible distinguishing between breastfed and formula-fed infants. Although there is a relatively recent systematic review on this topic (Iacovou 2012), the search took place in 2010 and excluded all unpublished and grey literature. We have also used a more recent review examining reported outcome measures within infantile colic, Steutel 2014, to ensure that our review examines an appropriate core outcome set (we consider this further within the Discussion). An up-to-date systematic review using Cochrane methodology was therefore required.

OBJECTIVES

To assess the effects of dietary modifications for reducing colic in infants less than four months of age.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

Infants younger than four months of age suffering from infantile colic (whether breastfed or formula-fed), as defined by the study. Both breastfed and formula-fed infants were eligible.

Types of interventions

This review sought to compare any one of the following dietary interventions, alone or in combination, versus another intervention(s) or placebo.

Breastfed infants

1. An educational intervention that supports and directs a specific dietary modification to modify the mother's diet by excluding certain components such as milk, yogurt, cheese and other foods
2. Low-allergen maternal diet
3. Diet plan or dietary supplementation, regardless of duration of intervention

Formula fed infants

1. Soy-based formula
2. Extensively hydrolysed formula based on whey or casein
3. Partially hydrolysed formula
4. Formula with low or no content of lactose
5. Amino-acid based formula
6. Formula that includes prebiotics

We excluded studies involving probiotics. For further information on these interventions, please see Praveen 2014.

Types of outcome measures

Primary outcomes

1. Duration of crying* (postintervention versus baseline or postintevention). Data could have been continuous (for example, hours per day), or dichotomous (for example, reduction under a predefined threshold, as determined by the study authors). Data must have been collected prospectively, not through retrospective recollection at the end of the study period, using methods such as parent diaries, video or audio recordings, or actigraphy.

Secondary outcomes

1. Number of responders in each group after treatment*. Responders were defined as those who experienced a decrease in daily crying, as reported by the study authors (dichotomous outcome).
2. Frequency of crying episodes per 24 h* (postintervention versus baseline) (continuous outcome)
3. Parental or family quality of life, including measures of parental stress, anxiety or depression* (continuous outcome)
4. Infant sleep duration per 24 h at 7, 14, and 21 days* (postintervention versus baseline) (continuous outcome)
5. Parental satisfaction*, measured by Likert scales or a numeric rating scale (continuous outcome)
6. Adverse effects to dietary modifications: constipation*, vomiting*, diarrhoea, apnoea, apparent life-threatening events and lethargy (dichotomous outcome). We analysed the frequency of all adverse effects in each study group.

We included outcomes evaluated after the completion of any treatment protocol (that is, any period, any number of treatments), and also at later follow-up, when reported.

We used those outcomes indicated by an asterisk (*) to populate the 'Summary of findings' table for the main comparison, 'dietary interventions for infantile colic versus placebo or other interventions', where data permitted.

Search methods for identification of studies

Electronic searches

We searched the databases and trials registers listed below up to July 2018 using the strategies in Appendix 1. We imposed no restrictions on publication date or language.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6) in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register (searched 9 July 2018).
2. MEDLINE Ovid (1946 to June week 5 2018).
3. MEDLINE In-Process & Other Non-Indexed Citations Ovid (searched 9 July 2018).
4. MEDLINE Epub Ahead of Print Ovid (searched 9 July 2018).
5. Embase Ovid (1974 to 2018 week 28).
6. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 to 10 July 2018).
7. PsycINFO Ovid (1806 to July week 1 2018).
8. Science Citation Index Web of Science (SCI; 1970 to 10 July 2018).
9. Social Sciences Citation Index Web of Science (SSCI; 1970 to 10 July 2018).
10. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 to 10 July 2018).
11. Conference Proceedings Citation Index - Social Sciences & Humanities Web of Science (CPCI-SS&H; 1990 to 10 July 2018).
12. *Cochrane Database of Systematic Reviews* (CDSR; 2018, Issue 7), part of the Cochrane Library (searched 9 July 2018).
13. Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2, Final issue), part of the Cochrane Library (searched 6 January 2016).
14. LILACS (Latin American and Caribbean Health Science Information database; search.bvsalud.org/portal/?lang=en; searched 10 July 2018).
15. IBECS (ibecs.isciii.es/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=IBECS&lang=i&form=F; searched 10 July 2018).
16. HomeoIndex (bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=HomeoIndex&lang=i&form=F; searched 10 July 2018).
17. Networked Digital Library of Theses and Dissertations (NDLTD; www.ndltd.org; searched 10 July 2018).
18. TROVE (limited to Australian theses; trove.nla.gov.au; searched 10 July 2018).
19. WorldCat (limited to theses; worldcat.org; searched 10 July 2018).
20. PubMed Dietary Supplement Subset (ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx; searched 10 July 2018).
21. ClinicalTrials.gov (clinicaltrials.gov; searched 10 July 2018).
22. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; apps.who.int/trialsearch; searched 10 July 2018).

Searching other resources

We searched the bibliographies of included studies to identify any other potentially relevant studies. On 9 July 2018, we searched Google (www.google.com) for grey literature, using the terms 'Infantile colic AND (diet OR formula) AND randomised controlled trial'. We handsearched conference proceedings from the ESPGHAN annual scientific meetings from the past five years (from 2013 to 2018) to identify other potentially relevant studies that may not be published in full. Where we identified references to relevant unpublished or ongoing studies, we recorded them and made attempts to obtain sufficient information so as to incorporate them in the review. Where data were not complete, we contacted the study authors in order to verify the eligibility of the study.

Data collection and analysis

We were unable to use all pre-planned methods, those not used have been summarised in 'Differences between protocol and review' section.

Selection of studies

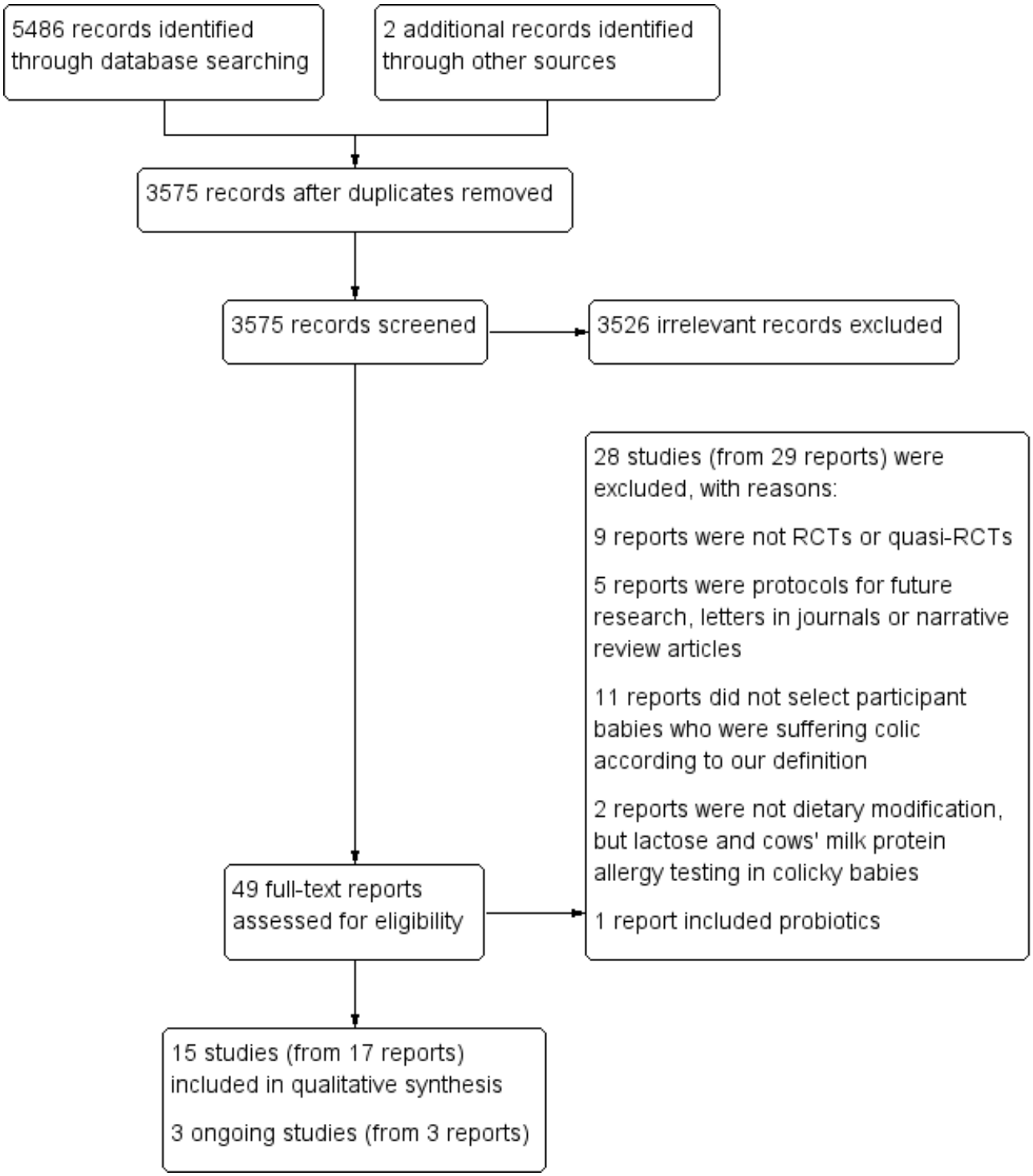
Two reviewers (SB and MG) independently screened titles, abstracts, and full reports for eligibility against the inclusion criteria (see Criteria for considering studies for this review). Specifically, they:

1. merged search results using reference management software and removed duplicate records of the same report;
2. examined titles and abstracts to remove irrelevant reports;
3. retrieved full texts of potentially relevant reports;
4. linked together multiple reports of the same study;
5. examined full-text reports for studies that met the eligibility criteria;
6. corresponded with investigators, when appropriate, to clarify study eligibility;
7. at all stages, noted reasons for inclusion and exclusion of reports, resolving any disagreements through consensus;
8. made final decisions on study inclusions and resolved any discrepancies through a process of consensus;
9. proceeded to data collection.

As Pitkin 1999 discusses, there are issues of the accuracy with which abstracts reflect the published report, so although we searched conference abstracts for possible studies to include, we excluded stand-alone abstract publications from our review; that is, we only included abstract publications that related to a study for which we also had a full-text report. See Differences between protocol and review.

We recorded the outcomes of our decisions in a PRISMA diagram (Moher 2009). See Figure 1.

Figure 1. Study flow diagram.



Data extraction and management

We developed data extraction forms a priori, as per the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We then extracted, where possible, information on the following.

1. Characteristics of participants: source of participants, inclusion and exclusion criteria, total number at baseline, total number at completion, setting, definition of 'colic' applied, diagnostic criteria applied, type of feeding (breastfeeding, formula feeding), age at onset of colic, age at commencement of intervention, and potential effect modifiers such as sex.
2. Interventions and controls: number of groups, intervention(s) applied, frequency and duration of treatment, total number of treatments, and concomitant use of pacifier.

3. Methods: study design, duration, sequence generation, allocation concealment, blinding of outcome assessors, and evaluation of success of blinding.
4. Outcomes: list of outcomes assessed, definitions used, and values of means and standard deviations at baseline and at time points defined by the study protocol (or change from baseline measures, if given).
5. Results: outcome measures, follow-up data (including means and standard deviations, standard errors, or confidence intervals (CI) for continuous data, and summary tables for dichotomous data), withdrawals, and losses to follow-up.
6. Other: references to other relevant studies, points to follow-up with study authors, comments from the study authors, key conclusions from the study (by the study authors), other comments from the review authors.

Two review authors (SB; MG) extracted the data independently using the data extraction form. A third review author (FS) resolved any persisting disagreements, which occurred on two occasions. We collated the data in the latest version of Review Manager 5 (RevMan 5) (RevMan 2014).

Assessment of risk of bias in included studies

Using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017), two review authors (SB; MG) independently evaluated each study for risk of bias within each of the following domains: sequence generation; allocation concealment; blinding of parents and health professionals; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity, which included consideration of potential risks due to changing methods of data collection (such as different ways of recording crying). They judged each domain as being at low, high, or unclear risk of bias using the criteria described in Appendix 2, compared the judgments, and discussed and resolved any inconsistencies in their assessments. A third review author (FS) was available to resolve any persisting disagreements, had there been any.

Measures of treatment effect

Dichotomous data

We were unable to conduct any meta-analyses and instead provided narrative descriptions of the results. For planned methods see Differences between protocol and review.

Continuous data

We were unable to conduct any meta-analyses and instead provided narrative descriptions of the results. For planned methods see Differences between protocol and review.

Unit of analysis issues

For each included study, we determined whether the unit of analysis was appropriate for the unit of randomisation and the design of that study (that is, whether the number of observations matched the number of units that were randomised (Deeks 2017).

Studies with multiple treatment arms

We were unable to conduct any meta-analyses and instead provided narrative descriptions of the results. For planned methods see Differences between protocol and review.

Cross-over studies

We were unable to conduct any meta-analyses and instead provided narrative descriptions of the results. For planned methods see Differences between protocol and review.

Dealing with missing data

Where data were missing, we contacted the corresponding authors of included studies, requesting them to supply any unreported data. Where it was not possible to obtain the missing data, we recorded this on the data collection form, reported it in the 'Risk of Bias' table, and discussed the extent to which the missing data might have altered the results and, hence, the conclusions of the review. For included studies, we noted levels of attrition.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by comparing the distribution of important participant characteristics between trials (age or presence of prematurity, length of symptoms at recruitment) and trial characteristics (randomisation, concealment, blinding of outcome assessment, losses to follow-up, treatment type, cointerventions).

Assessment of reporting biases

In order to minimise publication bias, we attempted to obtain the results of any unpublished studies, to compare the results extracted from published journal reports with the results obtained from other sources (including any correspondence).

Data synthesis

We were unable to conduct any meta-analyses, for planned methods see Differences between protocol and review.

Subgroup analysis and investigation of heterogeneity

We were unable to conduct any meta-analyses and thus subgroup analyses were not possible. For planned subgroup analyses see Differences between protocol and review.

Sensitivity analysis

We were unable to conduct any meta-analyses and thus sensitivity analyses were not necessary. For planned methods see Differences between protocol and review.

Summary of findings table

We assessed the overall quality of the evidence for the following outcomes measured at postintervention using the GRADE approach (Guyatt 2008): duration of crying; number of responders in each group after treatment; frequency of crying episodes per 24 h; parental or family quality of life, including measures of parental stress, anxiety or depression; infant sleep duration per 24 h at 7, 14, and 21 days; parental satisfaction; and adverse effects to dietary modifications: constipation and vomiting. The GRADE approach appraises the quality of evidence based on the extent to which one can be confident that an estimate of effect, or association, reflects the item being assessed. RCTs start as high-quality evidence, but

may be downgraded due to: risk of bias (methodological quality), indirectness of evidence, unexplained heterogeneity, imprecision (sparse data), and publication bias. We determined the overall quality of the evidence for each outcome after considering each of these factors, and graded them as follows.

1. High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
2. 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.
3. Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. 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.

We reported our quality ratings in a 'Summary of findings' table, which we constructed using GRADEpro GDT (GRADEpro GDT 2015), for the comparison, 'dietary interventions for infantile colic versus placebo or other interventions'.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies.

Results of the search

Our electronic searches yielded 5486 records up to 10 July 2018; we found two additional records from searching other sources. After removing duplicates, two review authors independently screened 3575 titles and abstracts for relevance, excluding 3526. Of the 49 records brought forward for full-text review, we excluded 29 records reporting on 28 studies (Characteristics of excluded studies), and included 17 records reporting on 15 studies (Characteristics of included studies). The three remaining reports relate to three ongoing studies (Characteristics of ongoing studies). See Figure 1.

Included studies

This review includes 15 studies involving a total of 1121 participants (Campbell 1989; Forsyth 1989; Hill 1995; Hill 2005; Jakobsson 2000; Kanabar 2001; Kearney 1998; Lothe 1987; Lucassen 2000; Miller 1990; Oggero 1994; Savino 2005; Savino 2006; Taubman 1988; Treem 1991). See Characteristics of included studies tables.

Study design

All 15 studies were RCTs, and of these, seven used a cross-over design (Forsyth 1989; Jakobsson 2000; Kanabar 2001; Kearney 1998; Lothe 1987; Miller 1990; Treem 1991). In this review, we found both cross-over trials that did not provide an adequate washout period and cross-over trials that provided separate data for the first arm.

Setting

Three studies took place in Turin, Italy (Oggero 1994; Savino 2005; Savino 2006), while two apiece were in Connecticut, USA (Forsyth 1989; Treem 1991); Melbourne, Australia (Hill 1995; Hill 2005); and Malmö, Sweden (Jakobsson 2000; Lothe 1987). One study took place in Amsterdam, Netherlands (Lucassen 2000); Cork, Ireland (Kearney 1998); London, UK (Kanabar 2001); Pennsylvania, USA (Taubman 1988); Scotland, UK (Campbell 1989); and Sydney, Australia (Miller 1990).

Participants were recruited from outpatient services.

Participants

The age of participants ranged from 2 weeks in Hill 2005 to 16 weeks in Hill 1995.

Participants were diagnosed with colic on enrolment. The specific criteria for a diagnosis of colic varied between studies, as did the minimum length of symptoms required to make a diagnosis of infantile colic. Most studies (87.5%) used a definition of colic consistent with the Wessel criteria (Wessel 1954).

The studies excluded children with organic causes for their pathology (see Characteristics of included studies tables).

Interventions

The duration of initial dietary intervention varied from 4 days in Forsyth 1989 to 21 days in Savino 2005.

The dietary modifications included: changes to the maternal diet (Hill 1995; Hill 2005; Oggero 1994); extensively hydrolysed formula (Forsyth 1989; Hill 1995; Jakobsson 2000; Lucassen 2000; Taubman 1988); a partially hydrolysed, lower lactose, whey-based formula with oligosaccharide (Savino 2006); the use of simethicone (Savino 2006); addition of lactase enzyme to the infant's standard milk (Kanabar 2001; Kearney 1998; Miller 1990); phytotherapeutic agents (Savino 2005); soy formula (Campbell 1989; Lothe 1987); or soy formula with polysaccharide (Treem 1991).

Outcomes

Below, we present the key outcomes that studies reported, as shown in Summary of findings for the main comparison.

1. Duration of crying (Campbell 1989; Forsyth 1989; Lucassen 2000; Jakobsson 2000; Oggero 1994; Savino 2005).
2. Number of responders in each group after treatment (Campbell 1989; Hill 2005; Oggero 1994).
3. Frequency of crying episodes per 24 h (Taubman 1988; Savino 2006).
4. Adverse effects to dietary modifications (Kanabar 2001; Kearney 1998; Lucassen 2000; Miller 1990; Savino 2005; Savino 2006).

Funding

Four studies reported public funding and stated that there had been no financial involvement with industry (Campbell 1989; Jakobsson 2000; Oggero 1994; Savino 2005). The manufacturing companies of the study intervention sponsored three studies, but the study authors confirmed via email that industry had no involvement in the conduct of the studies or the writing up of the results (Lucassen 2000; Miller 1990; Savino 2006). The manufacturers of the intervention supported eight studies in some way (Forsyth 1989; Hill 1995; Hill 2005; Kanabar 2001; Kearney 1998; Lothe 1987; Taubman 1988; Treem 1991).

Excluded studies

We excluded 28 studies for various reasons, as summarised below.

1. Nine studies were not RCTs or quasi-RCTs (Arikan 2008; Bellaiche 2018; Evans 1981; Iacono 1991; Imanieh 2004; Jakobsson 1983; Nocerino 2012; Savilahti 1989; Xinias 2017).
2. Five studies were letters in journals or narrative review articles (Buchanan 1998; Gerrard 1984; Koonce 2011; Laws 1991; Sargsyan 2006).
3. Eleven studies did not select participating infants who were suffering colic before the study but included normal infants (Barr 1991; Berseth 2009; Campeotto 2011; Giovannini 2014; Iacovou 2018; Infante 2011; Rozé 2012; Savino 2003; Sherman 2015; Vandenplas 2017; Vivatvakin 2010). As this is a review of treating established colic, we excluded such studies.
4. Two studies were not of dietary modification, but of lactose and cows' milk protein allergy testing in colicky babies (Liebman 1981; Pärtty 2015).
5. One study was of probiotics (Dupont 2010).

Ongoing studies

There are three ongoing studies, which are all double-blind RCTs.

NCT01721850 is in healthy infants of 35 to 42 weeks gestational age and 15 to 60 days old, with a Wessel diagnosis of colic (Wessel 1954). There will be a parallel assignment with three arms: control formula (standard formula), intervention formula one (infant formula with hydrolysed protein (type I) and pre- and probiotics), intervention formula two (infant formula with hydrolysed protein (type II) and pre- and probiotics).

NCT02813772 is enrolling full-term infants with a diagnosis of "1C according to Rome III criteria" (quote). There will be a parallel assignment: a partially hydrolysed formula with reduced lactose content and*Lactobacillus reuteri* versus a standard formula.

NCT03329222 is enrolling full-term infants diagnosed with colic and comparing a standard formula versus hydrolysed formula.

Risk of bias in included studies

Please see the 'Risk of bias' tables, beneath the Characteristics of included studies tables, for more information of the risk of bias in the included studies. Please also see Figure 2 and Figure 3 for a graphic summary of the risk of bias in the included studies.

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

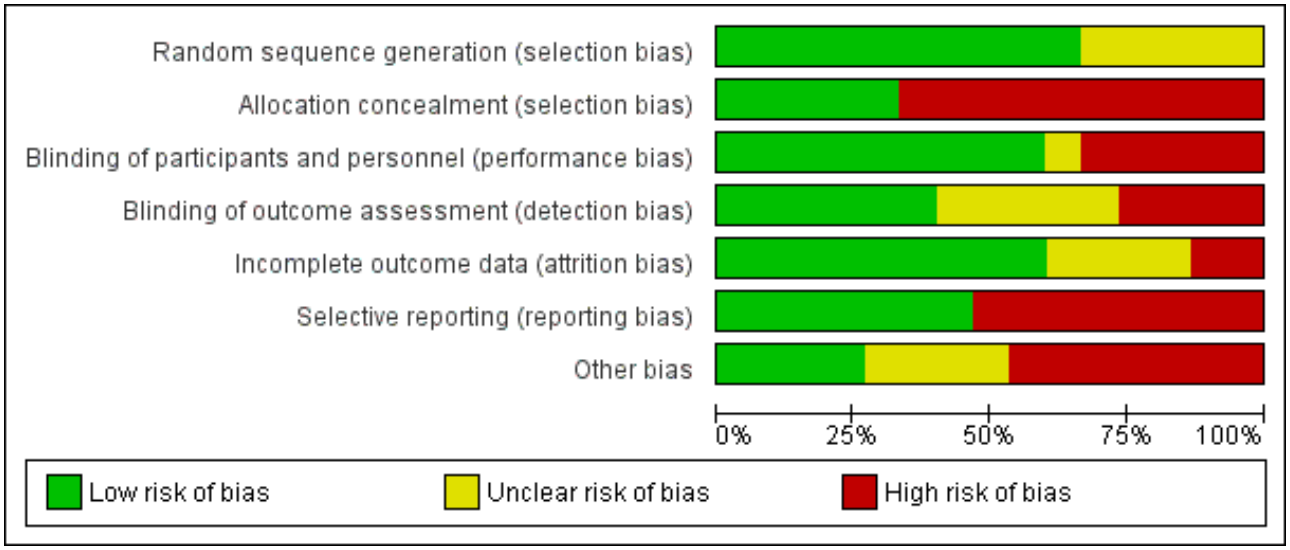
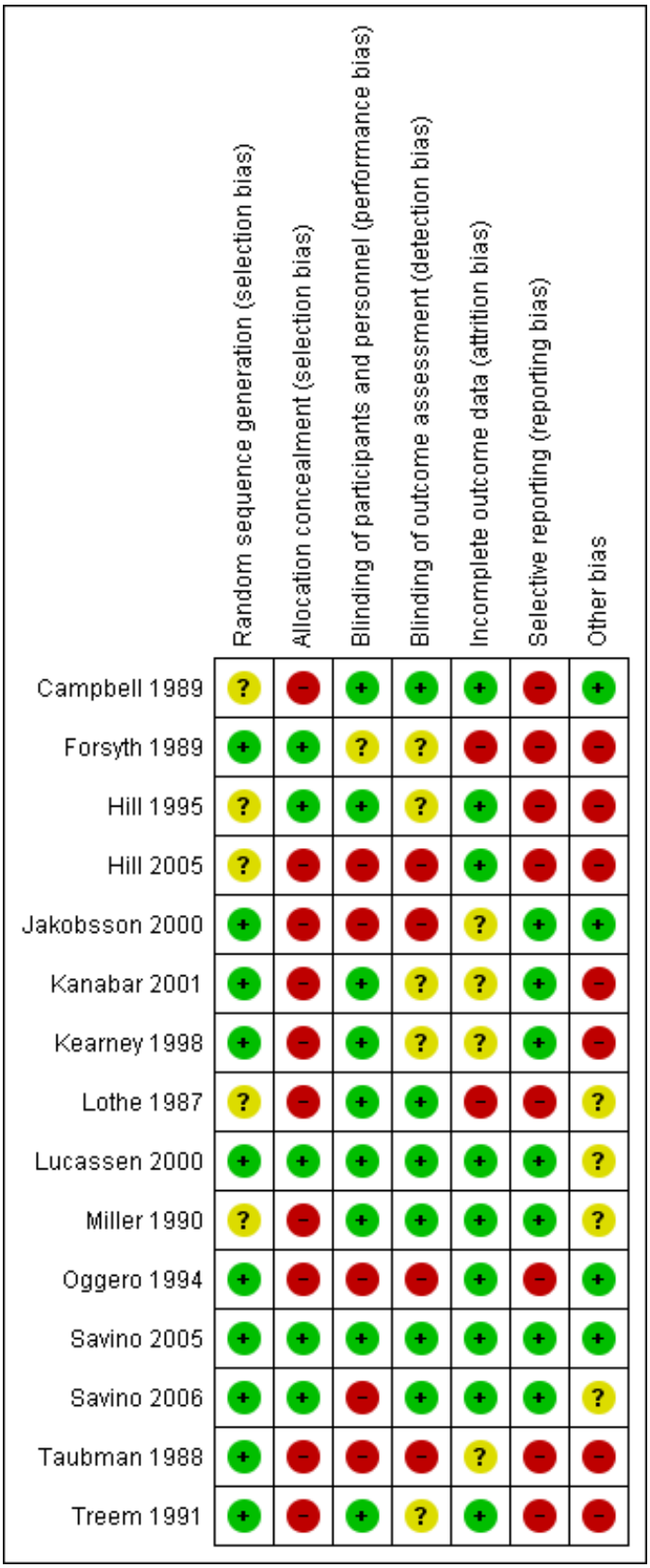


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

We considered nine studies to be at low risk of selection bias based on the published report (Forsyth 1989; Jakobsson 2000; Kanabar 2001; Kearney 1998; Oggero 1994; Savino 2005; Savino 2006; Taubman 1988; Treem 1991). In Lucassen 2000, the lead author responded to a request for more information and confirmed adequate sequence generation. The five remaining studies did not describe the method of randomisation, so we judged these studies to be at unclear risk of selection bias for this domain (Campbell 1989; Hill 1995; Hill 2005; Lothe 1987; Miller 1990).

Allocation concealment

We rated five studies at low risk of bias: four studies adequately described allocation (Forsyth 1989; Hill 1995; Savino 2005; Savino 2006), and the lead author of one study, Lucassen 2000, responded to a request for more information and confirmed adequate allocation concealment. We judged the 10 remaining studies to be at high risk of bias because the allocation concealment was not reported (Campbell 1989; Hill 2005; Jakobsson 2000; Kanabar 2001; Kearney 1998; Lothe 1987; Miller 1990; Oggero 1994; Taubman 1988; Treem 1991).

Blinding

Performance bias

We rated nine studies to be at low risk of performance bias (Campbell 1989; Hill 1995; Kanabar 2001; Kearney 1998; Lothe 1987; Miller 1990; Lucassen 2000; Savino 2005; Treem 1991). Authors of eight of these studies described adequate methods for blinding participants and personnel (Campbell 1989; Hill 1995; Kanabar 2001; Kearney 1998; Lothe 1987; Miller 1990; Savino 2005; Treem 1991), while for Lucassen 2000, again the lead author responded to a request for more information and confirmed adequate blinding of participants and personnel. One study reported the use of blinding but did not describe it clearly (Forsyth 1989), so we rated it at unclear risk of performance bias. We rated five studies at high risk of performance bias; four because they did not adequately describe blinding of participants and personnel (Hill 2005; Jakobsson 2000; Oggero 1994; Taubman 1988), and one, Savino 2006, because it was impossible to blind participants owing to the nature of the intervention and the control (simethicone had to be administered to the infant separately).

Detection bias

We rated six studies at low risk of detection bias (Campbell 1989; Lothe 1987; Lucassen 2000; Miller 1990; Savino 2005; Savino 2006). Five of these studies described adequate methods for blinding of outcome assessment (Campbell 1989; Lothe 1987; Miller 1990; Savino 2005; Savino 2006), while the lead author of Lucassen 2000 confirmed adequate blinding by correspondence. Five studies reported the use of blinding but did not describe it clearly, so we judged these studies to be at unclear risk of detection bias (Forsyth 1989; Hill 1995; Kanabar 2001; Kearney 1998; Treem 1991). We rated four studies at high risk of detection bias because they did not describe blinding of outcome assessment adequately (Hill 2005; Jakobsson 2000; Oggero 1994; Taubman 1988).

Incomplete outcome data

We judged two studies to be at high risk of attrition bias because the details of dropouts were not clear from the report, and there was only partial information as to which group they were from (Forsyth 1989; Lothe 1987). Whilst some inference for an intention-to-treat analysis is possible, further details were not available from the study authors. We rated four studies at unclear risk of attrition bias because they did not adequately describe dropouts (Jakobsson 2000; Kanabar 2001; Kearney 1998; Taubman 1988). We judged the remaining nine studies to be at low risk of attrition bias because dropouts were balanced across treatment groups, with similar reasons for withdrawal and few dropouts (Campbell 1989; Hill 1995; Hill 2005; Lucassen 2000; Miller 1990; Oggero 1994; Savino 2005; Savino 2006; Treem 1991).

Selective reporting

We rated eight studies as being of high risk of reporting bias, as the study authors did not report at all on adverse effects, did not have a protocol or did not supply us with the information (Campbell 1989; Forsyth 1989; Hill 1995; Hill 2005; Lothe 1987; Oggero 1994; Taubman 1988; Treem 1991). We judged the remaining seven studies to be at low risk of reporting bias, either because it was specifically stated in the report of the study that there were no adverse effects (Jakobsson 2000; Kanabar 2001; Kearney 1998; Savino 2005) or the study authors confirmed that this was the case through correspondence (Lucassen 2000; Miller 1990; Savino 2006).

Other potential sources of bias

Because of the nature of the evidence contained within these studies, and the claims for one product or intervention over another in such a vulnerable population, we considered any involvement by the companies supplying or manufacturing the intervention product in the conduct of the studies or the writing up of results to trigger a rating of high risk of other bias.

We considered four studies that stated no financial involvement with industry, whether by provision of experimental product or direct financial support for the work, to be at low risk of bias (Campbell 1989; Jakobsson 2000; Oggero 1994; Savino 2005). We judged a further three studies to be at unclear risk of bias as they were sponsored by the manufacturing companies of the study intervention, but we received confirmation that industry had no involvement in the conduct of the studies or the writing up of the results (Lucassen 2000; Miller 1990; Savino 2006). We rated the remaining eight studies at high risk of bias as they stated that they were supported in some way by the manufacturers of the intervention or related products (Forsyth 1989; Hill 1995; Hill 2005; Kanabar 2001; Kearney 1998; Lothe 1987; Taubman 1988; Treem 1991).

None of the studies appeared to have any other potential sources of bias other than industry funding.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: dietary interventions for infantile colic versus placebo or other interventions

Below, we present the results for each combination of dietary regimen and comparison, by assessed outcome and colic type, with the exception of those studies for which we could not extract data.

Despite the significant number of studies, there was no opportunity to complete a meta-analysis due to a combination of heterogenous outcome measures, grouping of different populations in reports of results, and lack of reporting on key outcomes (in particular, adverse effects) and summary outcome statistics. Thus, we provide a narrative description of the results. We report exact P values, where available, from the primary studies; where these were not available, we reported the figure given. We report the GRADE rating throughout. However, as the same two key issues affect all studies (imprecision due to very small sample sizes and risk of bias across all criteria), we do not make special mention of these within each comparison. See Summary of findings for the main comparison.

1. Low-allergen maternal diet versus a diet containing known potential allergens

Two studies (205 infants) by the same team in Australia examined the effect of modifying breastfeeding mothers' diets to control for proteins or other substances that might be triggering symptoms of colic (Hill 1995; Hill 2005). However, we were unable to combine the data from these studies in a meta-analysis because Hill 1995 grouped together breastfed babies whose mothers' diets were modified and formula-fed babies whose own diet was modified to remove the proteins. Authors did not report separate data for breastfeeding mothers only, and the study authors did not respond to our request for these data.

Primary outcome: duration of crying

Neither study reported data on this outcome (Hill 1995; Hill 2005).

Secondary outcomes: number of responders in each group after treatment

Hill 2005 (90 infants) reported a significant difference (37% difference; 95% CI 18 to 56; P < 0.001) in responders (i.e. reduction in cry/fuss duration of 25%). This occurred in the low-allergen group in 35/47 babies, compared with 16/43 babies in the control group. The low-allergen diet excluded all dairy products, soy, wheat, eggs, peanuts, tree nuts and fish, and included a rice milk drink, meat, vegetables, fruit, corn and rice, as well as a calcium supplement and rice-based bread. We rated the quality of this evidence as very low due to risk of bias and imprecision (Summary of findings for the main comparison).

Neither study assessed our other secondary outcomes: frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h, parental satisfaction or adverse effects to the dietary modifications.

2. Low-allergen diet or soy milk formula versus standard diet or cow's milk formula and dicyclomine hydrochloride

Only one study (120 infants) contributed data to this comparison (Oggero 1994). It compared a restricted, low-allergen diet in breastfeeding mothers or soy milk in formula-fed babies versus the addition of dicyclomine hydrochloride (a pharmacological treatment for stomach spasms) for both breastfed and formula-fed infants in the treatment group who also had normal diet, over a period of 30 days.

Primary outcome: duration of crying

Authors did not specifically report duration of crying at end of intervention.

Secondary outcomes: number of responders in each group after treatment

Oggero 1994 reported data on this outcome, but investigators used stricter rules for classifying 'improvement' compared to our protocol (Savino 2014), stating "A positive result was defined as a reduction of crying to less than one hour per day after 48 hours of treatment, with remission persisting for one month". The study found that 10/15 (66.6%) breastfed babies responded to dicyclomine hydrochloride and a normal diet, compared with 10/16 (62.5%) on a low-allergen diet, while 24/45 (53.3%) formula-fed babies on dicyclomine improved compared with 29/44 (65.9%) on a low allergen formula.

The study did not assess our other secondary outcomes: frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h, parental satisfaction or adverse effects.

3. Hydrolysed formula versus standard formula

Three studies (185 infants) compared an extensively hydrolysed cows' milk formula with standard cows' milk formula (Forsyth 1989; Hill 1995; Lucassen 2000). The Hill 1995 study did not separate the results for breastfed and formula-fed infants and the study author provided no further details in response to our request. The Forsyth 1989 study (number of infants?) used a cross-over design. However, it was not clear from the reportwhether the results were from the first period alone or from the first and second cross-over periods combined, and the study authors did not respond to a request for further information, possibly due to the age of the study. Given this uncertainty, the Cochrane Developmental, Psychosocial and Learning Problems editorial team advised against combining these data in a meta-analysis, hence we provide a narrative description of the results of this study below.

Primary outcome: duration of crying

One study (43 participants), Lucassen 2000, reported that the number of infants crying for less than 3 hours per day on at least 3 days a week following the intervention was 8/23 in the whey hydrolysate group versus 5/20 in the standard formula group (χ^2= 0.20, P = 0.65).

The same study reported continuous data on this outcome (Lucassen 2000), demonstrating a greater reduction in crying time postintervention with the hydrolysed formula (104 min/d, 95% CI 55 to 155) than with the standard formula (3 min/d, 95% CI −63 to 67); difference = 101 min/d 95% CI = 25 to 179; P = 0.02). We rated the quality of the evidence as very low (Summary of findings for the main comparison).

Secondary outcomes: adverse effects

Lucassen 2000 did not report on adverse effects, but we received further information from the study author indicating that there were no adverse effects. The other two studies did not report on adverse effects either, so it was not possible to conduct an analysis of any adverse effects or causes of dropouts from the studies from use of the hydrolysed formulas (Forsyth 1989; Hill 1995). We rated the quality of the evidence as very low (Summary of findings for the main comparison).

None of the three studies assessed our other secondary outcomes: number of responders in each group after treatment, frequency of

crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h or parental satisfaction.

4. Hydrolysed formula versus another hydrolysed formula

One study (22 infants) was designed as a cross-over trial, with each infant receiving both types of formula for a week (Jakobsson 2000). In this study, 10 infants were randomised to receive Alimentum (manufactured by Abbott) and 12 infants to receive Nutramigen (manufactured by Mead Johnson).

Primary outcome: duration of crying

The study authors concluded that both hydrolysed formulas were equally effective in resolving symptoms for babies in the trial who were started on standard formula. However, no separate data from the period before the cross-over period are provided by the authors, therefore we could not use this outcome data. We rated the quality of this evidence as very low (Summary of findings for the main comparison).

Secondary outcomes: adverse effects

The study authors monitored a number of possible adverse effects, including vomiting and stool consistency. Two patients were withdrawn from the Nutramigen group; one due to vomiting and another due to loose stools. Stool consistency did not differ between the two study periods; however, infants experienced a significant increase in incidence of liquid stools from baseline only when fed Nutramigen.

The study did not assess any of our secondary outcomes: number of responders in each group after treatment, frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h, parental satisfaction.

5. Hydrolysed formula or dairy- and soy-free maternal diet versus standard diet/formula and parental education or counselling

One study (21 participants) reported data on this comparison (Taubman 1988). One group received education and training with normal diet and thea second received no training, but either hydrolysed formula or maternal milk-free diet.

Primary outcome: duration of crying

Taubman 1988 found that duration of crying per 24 h in the hydrolysed or dairy- and soy-free group (N = 10) decreased to 2.03 h (SD 1.03) by nine days into the intervention (P = 0.01). In the parent education or counselling group (N = 10), the crying of babies per 24 h decreased to 1.08 h (SD 0.7) after nine days (P = 0.001). We rated the quality of this evidence as very low (Summary of findings for the main comparison).

Secondary outcomes

The study did not assess any other of our secondary outcomes: number of responders in each group after treatment, frequency of crying episodes per 24 hours, parental or family quality of life, infant sleep duration per 24 h, parental satisfaction or adverse effects.

6. Partially hydrolysed, lower lactose, whey-based formula containing oligosaccharide versus standard formula with simethicone

One study (267 infants) analysed the effectiveness of a partially hydrolysed, whey-based formula containing a mixture of oligosacharides, low lactose level, modified vegetable oil and starch versus a standard formula (as used by parents) with simethicone for infantile colic (Savino 2006).

Primary outcome: duration of crying time

Savino 2006 did not report data on this outcome.

Secondary outcomes

Frequency of crying episodes per 24 h

Savino 2006 found that infants (N = 130) receiving the partially hydrolysed formula had a significant decrease (95% CI −0.7 to −1.8) in colic episodes after one week (2.47 episodes (SD 1.94) at day 7 versus 5.99 episodes (SD 1.84) at study entry) compared with infants (N = 137) receiving the standard formula (3.72 episodes (SD 1.98) at day 7 versus 5.41 episodes (SD 1.88) at study entry). After two weeks, episodes of crying were significantly different (P < 0.001) between the two groups of infants (partially hydrolysed formula: 1.76 episodes (SD 1.60) versus standard formula: 3.32 episodes (SD 2.06)). We rated the quality of the evidence as very low (Summary of findings for the main comparison).

Adverse effects

Savino 2006 did not report data on adverse effects, but the lead author confirmed that these were assessed and recorded as part of the protocol, and that no infants experienced them.

The study did not report data on any of our other secondary outcomes: number of responders in each group after treatment, parental or family quality of life, infant sleep duration per 24 h or parental satisfaction.

7. Lactase enzyme supplementation versus placebo

Three studies (138 participants) investigated the addition of lactase enzyme to infant milk (Kanabar 2001; Kearney 1998; Miller 1990). Once again, due to significant heterogeneity of outcome reporting and limited data within the reports, as well as all three studies being cross-over trials that did not report data from before washout, we were unable to conduct a meta-analysis.

Primary outcome: duration of crying time

None of the three studies reported data on this outcome (Kanabar 2001; Kearney 1998; Miller 1990).

Secondary outcomes: adverse effects

Two studies reported that there were no adverse effects (Kanabar 2001; Kearney 1998), while the author of Miller 1990 confirmed via personal correspondence that this was the case.

The study did not report on our other secondary outcomes: number of responders in each group after treatment, frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h or parental satisfaction.

8. Extract of Foeniculum vulgare, Matricariae recutita, and Melissa officinalis versus placebo

One study (93 infants), Savino 2005, assessed the effectiveness and side effects of a phytotherapeutic agent versus placebo, both of which were administered twice a day for one week, in the treatment of infantile colic. The phytotherapeutic agent was a liquid containing extract of *Foeniculum vulgare* (fennel), *Matricariae recutita* (camomile) and *Melissa officinalis* (lemon balm), with vitamins B1, B5 and B6.

Primary outcome: duration of crying

Savino 2005 found that the average daily crying time of infants given the phytotherapeutic agent (N = 41) was 76.9 min/d at the end of the 1-week study (SD 23.5), compared with an average daily crying time of 169.9 min/d (SD 23.1) in infants given placebo (N = 47) (95% CI −102.89 to −83.11; P < 0.005). We rated the quality of the evidence as very low (Summary of findings for the main comparison).

Secondary outcomes: adverse effects

Savino 2005 reported that there were no serious adverse effects. They also reported episodes of vomiting (intervention = 8, placebo = 2; 95% CI 0.02 to 0.28; P = 0.06) and constipation (intervention = 4, placebo = 5; 95% CI −0.13 to 0.13; P = 0.72) for babies in the intervention (n = 41) and placebo (n = 47) groups. We rated the quality of this evidence as very low (Summary of findings for the main comparison).

Savino 2005 did not assess any of our other secondary outcomes: number of responders in each group after treatment, frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h or parental satisfaction.

9. Soy protein-based formula versus standard cows' milk protein-based formula

Two studies (84 infants) compared a soy protein-based formula with standard cows' milk protein-based formula (Campbell 1989; Lothe 1987). We were unable to conduct a meta-analysis as the outcomes were extremely heterogeneous.

In the cross-over study (65 infants) by Lothe 1987, study authors reported only aggregated results and did not respond to our request for data from the first arm only. Therefore, we are unable to consider the results any further.

Campbell 1989 (19 infants) compared duration of symptoms of colic following a single week on either a standard casein-based cows' milk protein formula (as control) or the same company's (Cow and Gate) soy formula. The study was run as a cross-over with all babies receiving both formulas over the space of two weeks. However, the data from the first phase were not presented separately and so was not included in this review.

Primary outcome: duration of crying

In Campbell 1989, mean crying time was lower in the soy protein-based formula group (12.7 h/week (SD 16.4); N = 10) than in the standard cows' milk protein-based formula group (17.3 h/week (SD 6.9); N = 9). We rated the quality of the evidence as very low (Summary of findings for the main comparison).

Secondary outcomes: number of responders in each group after treatment

Campbell 1989 reported 0/9 responders (0%) in the control group after therapy and 5/10 responders (50%) in the intervention group. We rated the quality of the evidence as very low (Summary of findings for the main comparison).

The study did not assess our other secondary outcomes: frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h, parental satisfaction or adverse effects.

10. Soy protein formula with polysaccharide versus standard soy protein formula

One study (27 infants) assessed this comparison (Treem 1991). Twelve babies received standard soy protein formula, and 15 babies received a formula supplemented with polysaccharide. As we did not receive a response from the study author to our request for pre-washout-phase data, we are unable to analyse these results.

Primary outcomes: duration of crying

Treem 1991 did not report data on this outcome.

Secondary outcomes

Treem 1991 did not present pre-washout-phase data to allow us to assess our secondary outcomes: number of responders in each group after treatment, frequency of crying episodes per 24 h, parental or family quality of life, infant sleep duration per 24 h, parental satisfaction or adverse effects.

DISCUSSION

Summary of main results

This review includes 15 studies, with a total of 1121 enrolled infants, that evaluated the effects of dietary modifications for treating infant colic. We were not able to perform any meta-analyses due to the heterogeneity of the studies and the outcomes that they measured.

The studies did not routinely report adverse effects, although a small number of study authors provided these data on request. There were also no studies reporting data on quality of life outcomes, which are of great interest to parents.

There is insufficient evidence to support the claims that soy protein benefits infants with fussiness and crying, in keeping with international guidelines (ESPGHAN) (Agostoni 2006), and that suggested soy milk formulas should not be used (see section Quality of the evidence below).

In sum, dietary modifications may or may not be useful or detrimental.

Overall completeness and applicability of evidence

The results of this review rest upon trials which, in general, were poorly designed, conducted and reported. Even though the studies were conducted in both university clinics and primary care hospitals in different countries, the applicability of the evidence to clinical practice is limited. Most dietary modifications explored by the trials, such as soy-based formula, were outdated, and clinical outcomes and data, such as adverse effects, were limited.

Moreover, heterogeneity was evident among definitions of colic. Studies were most often based on a small sample from a single centre, with no replication.

The number of infants included in the comparisons was low, ranging from 13 for lactase drops versus placebo, to 267 for partially hydrolysed, low-lactose, modified-oil, whey-based formula containing oligosaccharide and starch versus a standard formula with simethicone.

The small sample sizes do not reflect the large scale of the issue with infantile colic in our populations. In over 30 years of research included in this review, the studies we found are not robust enough to provide definitive answers regarding which – if any – dietary modification works. Nor do they shed any light on what colic is, a clearly symbiotically linked problem that also requires study. Most research apparently concentrates on testing specific products rather than the individual ingredients and their efficacy.

The outcome measures used are also of concern. As crying is a very subjective concept, objective methods of recording crying would be preferable. However, recording in diaries was the most common method, and this is a significant weakness in the utility of the evidence base. The use of 'treatment success' or 'responders' was also reported in a very heterogenous manner, and many of the specific thresholds reported bear little utility to parents or clinicians in real-life clinical situations.

Unfortunately, the included studies did not evaluate the impact of interventions on the quality of family life with the colicky infant. Validated questionnaires are available for parents (Sung 2014), and, in many ways, this is the most important set of measures for a self-limiting problem that does not necessarily require treatment but is treated to enhance outcomes for families. However, to date, investigators have failed to recognise the impact that symptoms of colic can have on parents' emotional state (Landgren 2010). This is a very sensitive issue because this clinical situation could damage the future parent-child relationship (Pauli-Pott 2000). In a recent systematic review of outcome measures reported in trials of infant colic, Steutel 2014 suggested a core set of measures that would address such issues. As the natural history of the condition is improvement, outcomes that measure the impact of symptoms whilst present are, in many ways, the most relevant, and the lack of reporting limits the applicability of the evidence.

In 2004 the UK's Chief Medical Officer, Sir Liam Donaldson, stated that soy-based formulas should be avoided for infants because of the "high phytoestrogen content, which could pose a risk to the long-term reproductive health of infants" (Donaldson 2004). This recommendation was based on "a 2003 report from the Committee on Toxicity (COT), an independent scientific committee that advises the Department of Health and other government agencies". It is unlikely, therefore, that studies would now consider soy formula at all and instead would go straight to extensively hydrolysed formula as the dietary modification for formula-fed babies (see Forsyth 1989; Hill 1995 and Lucassen 2000 above, and to some extent Taubman 1988 also). This limits the applicability of these earlier studies to current practice.

Quality of the evidence

We judged the quality of the evidence on the effectiveness of dietary modifications for infantile colic to be very low. This was particularly impacted by the high risk of bias in the design and conduct of studies, and a particular concern of publication bias linked to small study sizes, possibly associated with nutrition company sponsorship. Additionally, sample sizes were universally very small, with no power calculations, further downgrading quality for imprecision.

The lack of signalled adverse effects in the studies raises serious doubts about the quality, accountability and transparency of these trials. In any medical research, a researcher's first priority is to be accountable for exploring the effectiveness of different interventions while protecting the safety of patients. It is obviously preferable for researchers to contribute to improvements in the safety of healthcare interventions by recording all potential adverse effects. Collecting data on adverse effects in small children might require additional efforts, as researchers would often need to train caregivers to recognise and record potential adverse effects.

Given what has been said above, and the consequent low quality of the evidence, readers should exercise caution when interpreting the available data. Even if some results look positive (e.g. for hydrolysed protein formulas), it is possible that the advantages mentioned could simply be due to bias or chance. Based on the evidence presented, we cannot recommend hydrolysed protein formulas or other dietary modifications, and an allergen exclusion diet is no better than standard diet or placebo.

Potential biases in the review process

We conducted comprehensive searches, including extensive searches of the grey literature, to identify all relevant studies.

To avoid bias, two review authors (MG; SB) independently evaluated study eligibility, extracted data, assessed risk of bias and rated the quality of the evidence. On two occasions we resolved initial disagreements about inclusion or exclusion with another member of the team (FS). For the three studies in which one review author (FS) was involved (Oggero 1994; Savino 2006; Savino 2005), two other review authors (MG; SB) who did not participate in these studies evaluated study eligibility, extracted data, assessed risk of bias and rated the quality of the evidence.

As stated above, the quality of study reports in terms of detail, clarity, study flow, outcome reporting and availability of protocols, amongst many other factors, was variable and sporadic. In a number of circumstances, when study authors did not respond to our requests for further data, the reviewers had to interpret the data to the best of their ability. This may have introduced bias into the process.

Agreements and disagreements with other studies or reviews

We found three earlier reviews evaluating dietary modifications for infantile colic (Cohen-Silver 2009; Hall 2012; Perry 2011).

Cohen-Silver 2009 concluded that physicians can suggest a change to formulas containing whey hydrolysate for formula-fed infants, as well as maternal dietary modifications for breastfed infants. In our view, however, the conclusions appear to over-interpret the results of primary studies, not taking into account the poor quality of the evidence. Although Cohen-Silver 2009 underlines that exclusive hypoallergenic formula feeds should be reserved only for infants with a true allergy to cows' milk protein, change to hydrolysed

formulas cannot generally be advised to parents as routine clinical practice.

Hall 2012 is a systematic review of studies of several nutritional interventions such as high-fibre formula, low-allergenic formula, lower allergenic maternal diet or the addition of lactase. Hall 2012 agreed with our review in that the quality of the research in this field must be recognised as a priority across different independent research groups.

Perry 2011 published a broad overview of all complementary and alternative medicines and nutritional supplements for the treatment of infantile colic. While we considered some of the trials in Perry 2011, they did not focus on dietary approaches with infant formulas or dietary modifications for breastfeeding mothers, so their scope was very different from ours. Also, their team concluded that there was no evidence to support clinical recommendations of any studied dietary intervention.

AUTHORS' CONCLUSIONS

Implications for practice

We have concluded the following.

1. It is not possible to draw any robust conclusions on the effectiveness of dietary modifications for infantile colic because the evidence is scant and prone to bias; presently, only a few trials are available, most of them outdated and at serious risk of bias.
2. Only one unreplicated study, with high risk of bias in several areas, found that parental education or counselling achieves a significant decrease in crying within the first three days compared to a dairy-free maternal diet or extensively hydrolysed formula.
3. It is not possible to draw any conclusions on the efficacy of dairy-free diets, soy-free diets, lactase enzyme supplementation of infant milk, or the addition of soy polysaccharide to standard soy protein formula.
4. Amongst studies examining the effect of an allergen-exclusion diet in breastfeeding mothers, we found a significant difference between responders in the low-allergen group versus the control group. However, because the quality of these studies is very poor, and the extent of the benefit observed is variable, readers should interpret these results with caution.
5. Available data show no difference between hydrolysed and standard infant formulas for colic; however, one study in our review stated that the two different hydrolysed protein formulas studied are equally effective in resolving symptoms.
6. Moreover, two different studies reported a reduction in symptoms of infantile colic with hydrolysed formulas in other comparisons: in the first study, a partially hydrolysed, low-lactose, modified-oil, whey-based formula containing oligosaccharide and starch showed a significant decrease in colic episodes compared with standard formula with simethicone. In the second study, hydrolysed formula relieved symptoms of colic after soy-based formula.
7. Given these interventions are not classified as medicinal products by regulatory bodies, there is a risk that an interventional dietary approach can be marketed to the public with a poor evidence base that would not occur for prescribed medicinal products. Thus, it is important to generate high-quality evidence to investigate such new milk formulas and, in the meantime, ensure the results of this review are used to guide current clinical practice and advice.

The implication for practice from this systematic review is that dietary modifications can be neither recommended nor excluded from therapies, given their unknown benefit, and that new research must address key methodological issues, some of which are context specific.

Implications for research

Current evidence on the effectiveness of dietary approaches for infantile colic is based mainly on old studies, which are usually affected by methodological limitations.

Future trials must align with clinically relevant outcomes about which there is a consensus regarding measurement methods and relevant time points. Reporting the resolution of colic, defined using up-to-date criteria for diagnosis, should be mandatory. Regarding crying time, objective measures using the host of audiovisual and other technologies that are cheaply available, should be considered essential to allow such assessment.

Other outcomes of importance to parents, such as crying time per day, parental quality of life and sleeping time should be reported, together with the data needed for synthesis. Adverse effects must be reported in a manner that recognises the different forms of such events (i.e. serious, minor and those requiring withdrawal of therapy). Given the natural history of the condition, a major challenge is to design trials that intervene early in the development of colic. Alternatively, subgroups will permit consideration of different patients based on age, for example, since a population pre-six weeks of age is, in many ways, very different from one that is post-six weeks of age.

More rudimentary methodological issues must also be addressed. Power calculations based on existing primary and secondary studies should be completed, as many of the studies we found were underpowered and of little value. Long-term outcomes should be considered, as this may allow economic evaluation in the future, given that many of the interventions being studied in this review are likely to be purchased directly by parents, and failure to address colic can lead to extra visits with medical staff or requirement for future medication.

Standardised tools for measuring outcomes that allow comparison and pooling of results across studies are needed for all outcomes, particularly given the new Rome IV criteria that refer to several elements in defining colic that are too subjective on their own to enable performance of sensible experimental studies (Drossman 2016). We would advise all future researchers to read this review in detail to identify primary works that may support study design. A recent published analysis of the existing tools being employed underlines the need to design and validate new assessment devices or scales for this clinical condition (García Marqués 2017), and this analysis should consider this existing evidence base in its entirety.

As indicated above, in planning new clinical trials, researchers should adopt a standard definition of infantile colic, such as the definition proposed by the Rome IV Committee (Benninga 2016; Drossman 2016; Wolke 2017), which includes the following diagnostic criteria for infantile colic: all of the following in infants from birth to four months of age: paroxysms of irritability, fussing or

crying that start and stop without obvious cause; episodes lasting three or more hours per day and occurring at least three days per week for at least one week; and no failure to thrive.

Given the growing evidence around the impact of infants' balance of gut microbiota on colic and other symptoms (Dubois 2016; Savino 2017), clear sample populations should include birth circumstances (i.e. vaginal versus caesarean), and feeding method (i.e. exclusive breastfeeding from birth versus exclusive formula feeding from birth). In addition, the populations for future trials should be separated, perhaps, into infants with a pre-existing family history of allergy to a certain dietary component (e.g. soy or cows' milk protein) versus those who do not.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Campbell 1989

Methods	Single-centre, double-blind, randomised controlled trial with 2 treatment groups
Participants	**Sample size**: 19 infants diagnosed with colic (0 dropped out) **Setting**: recruited in a single town (Livingston, West Lothian in Scotland, UK) **Sex**: 11 boys (58%), 8 girls (42%) **Mean age**: 7 weeks (SD not reported, range 3 to 14) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: formula fed (100%) **Birth order**: 4 first born, 7 second born, 8 third to sixth born **Inclusion criteria**: formula-fed infants with a clinical diagnosis were included in the study if they met the Wessel 1954 criteria **Exclusion criteria**: spontaneous remission in the observation week, colic not severe or already improving during baseline week. Does not specify that babies were 'otherwise well'; however, referral was via GP or HV who considered the baby to have infant colic
Interventions	**Intervention (n = 10)**: soy formula **Control (n = 9)**: standard formula **Duration**: 1 week
Outcomes	Mothers asked to complete a record sheet noting the amount of time of baby's colic symptoms each day. Record sheets scored by totaling all the periods of colic, to the nearest half hour, for 6 days of the week, omitting the first day of the week to allow for transition from previous milk
Notes	**Study start and end dates**: not recorded; however it was a 2-year study period and published in 1989 **COIs**: none stated **Funding source**: formula provided by Cow & Gate. Author was a GP, doing a research fellowship funded by the Health Service Research Committee of Scottish Home and Health Department **Adverse effects**: not reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "on the basis of random assignment" **Comment**: no further details given. Wrote to study author but received no response

Campbell 1989 *(Continued)*

Allocation concealment (selection bias)	High risk	**Comment**: no details given. Wrote to study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "control and intervention were packaged in identical coded tins"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "and the code of each pair of milks was not broken until the end of the ... period so that the observations would be double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: all data recorded. Accounted for all patients
Selective reporting (reporting bias)	High risk	**Comment**: no specific mention or reporting of adverse effects
Other bias	Low risk	**Comment**: not apparent

Forsyth 1989

Methods	Double-blind, randomised control trial with 2 treatment groups (cross-over study but we are using just the first trial)
Participants	**Sample size**: 32 infants (40 referred but 8 did not satisfy eligibility criteria) diagnosed with colic enrolled (15 dropped out: 6 did not begin taking the formula, 5 did not complete the diary and 4 discontinued the study after beginning it – specific groups not described) **Setting**: private practitioners and Department of Pediatrics, and Yale Child Study Center, New Haven, Connecticut, USA **Sex**: 11 boys (65%) **Mean age**: 5.38 weeks (SD 1.54, range 4 to 7) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: formula fed (100%) **Birth order**: not reported **Inclusion criteria**: aged 8 weeks or less at the time of enrolment, formula fed, crying reported 3 or more h/d, parents' subjective description of colic **Exclusion criteria**: any other causes of excessive crying
Interventions	**Intervention (n = 9)**: Nutramigen casein hydrolysate **Control (n = 8)**: ''a cow milk formula" (quote); 1 part Enfamil (standard formula) and 2 parts Nutramigen, to ensure blinding or alternative as per cross-over trial **Duration**: 4-day period and then crossed over

Forsyth 1989 *(Continued)*

Outcomes	Mothers recorded crying episodes in diaries and indicated which episodes they considered to have been caused by colic. Crying quantified in h/d
Notes	**Study start and end dates**: not reported, although this paper was written in early 1989 **COIs**: none specifically reported; however, study funded by manufacturers of the product that was used as the intervention **Funding source**: supported by a grant from Mead Johnson, whose products were used **Adverse effects**: not reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "random assignment table of random numbers"
Allocation concealment (selection bias)	Low risk	**Comment**: assignment by central pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment**: described as double-blind, but no details given and none received from study author
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment**: described as double-blind, but no details given and none received from study author
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment**: only partial details given on dropouts and which group they were from. Whilst some inference can be made for an intention-to-treat analysis, further details were not available from the study author
Selective reporting (reporting bias)	High risk	**Comment**: no specific mention or reporting of adverse effects. No response received from study author
Other bias	High risk	**Comment**: report says that cans of formula were prepared by Mead Johnson. No further details of involvement and no response received from study author

Hill 1995

Methods	Double-blind, randomised, placebo-controlled trial over 1 week with 4 treatment groups
Participants	**Sample size**: 38 formula-fed and 77 breastfed infants (36 dropped out – 18 in each group) **Setting**: metropolitan, community-based, well-infant centres, Melbourne, Australia **Sex**: not reported **Mean age**: not reported (SD not reported) **Mean weight**: not reported **Mean duration of colic (baseline)**: 5.1 h/d (SD 3.0) intervention, 5.9 h/d (SD 3.1) control

Hill 1995 *(Continued)*

	Mean crying (baseline): The mean day 1 total distress score for the intervention diet group was 330.5 minutes, and for the control diet group, 268.0 minutes (P = 0.12) **Feeding**: formula fed (33%; n = 38) **Inclusion criteria**: aged 4-16 weeks, uncomplicated pregnancy of more than 37 weeks' duration, uneventful perinatal period, colic definition 'rule of three', and otherwise healthy except for colic. Also included those on medication for colic, as long as medications continued throughout the trial **Exclusion criteria**: not reported
Interventions	**Intervention (n = 54)**: mothers of breastfed babies given a hypoallergenic or anti-oligogenic diet (excluding food dyes, additives, preservatives, milk, egg, wheat or nuts), and formula-fed babies provided with a casein based hydrolysate formula (Pregestamil) **Control (n = 61)**: mothers of breastfed babies given a standard oligoantigenic diet (avoiding food dyes, additives, preservatives), and formula-fed babies given standard formula (Enfamil Reduced Iron) **Duration**: 1 week
Outcomes	Parents instructed in the use of a 24-h distress score chart, which they were asked to complete on day 1 and day 8 of the trial, with distress marked in min/h
Notes	**Study start and end dates**: not reported; however, paper does report that the original study was intended to be 12 months, but that it was harder to recruit than they had expected and the study was finally closed after 3 years **COIs**: none reported **Funding source**: supported by a grant from Mead Johnson **Adverse effects**: none reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: says it is randomised. Wrote to study author but received no response
Allocation concealment (selection bias)	Low risk	**Comment**: sealed envelopes for assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: double-blind – identical sealed tins
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment**: as above
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: all patient outcomes described
Selective reporting (reporting bias)	High risk	**Comment**: no specific mention or reporting of adverse effects. No response received from study author

Hill 1995 *(Continued)*

Other bias	High risk	**Comment**: supported by a grant from Mead Johnson. No further details of involvement and no response received from study author

Hill 2005

Methods	Randomised controlled trial with 2 treatment groups
Participants	**Sample size**: 107 infants (17 dropped out – intervention = 6, control = 11) **Setting**: metropolitan, community-based, well-infant centres, Melbourne, Australia **Sex**: 54 boys (50%) 53 girls (50%) **Mean age**: 5.7 weeks (SD 1.1, range 2.9 to 8.6) **Mean weight**: not reported **Mean duration of colic (baseline)**: Mean distress duration at start of diet, in weeks intervention = 3.2 (range = 1 to 7), control = 3.4 (range = 1 to 6.0) **Mean crying (baseline)**: not reported **Feeding**: breastfed (100%) **Birth order**: not reported **Inclusion criteria**: < 6 weeks of age, breastfed, well-term infants (gestational age of > 37 weeks), normal singleton pregnancy, otherwise uneventful perinatal history and no perinatal morbidity other than distress, and presence of 'rule of three' crying in the week before presentation **Exclusion criteria**: mothers who were vegan, babies who were formula fed, spontaneous improvement
Interventions	**Intervention (n = 47)**: low-allergen diet without milk, soy, nuts, eggs, wheat and soy, but including a rice drink every day and rice bread **Control (n = 43)**: diet must have included milk, peanuts, egg, wheat, fish, tree nuts and soy every day **Duration**: 1 week
Outcomes	Detailed food diary by mothers, and recording of infant crying or fussing behaviour on a pre-validated chart, for 48 h on days 1, 2, 8 and 9
Notes	**Study start and end dates**: 2000 (start) to 2002 (end) **COIs**: not reported but see funding source directly below **Funding source**: financed by the Rice Growers' Co-operative, Australia. Intervention was rice milk and rice bread **Adverse effects**: none reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "referred to the Department of Allergy for diet randomisation" **Quote**: "assigned to one of the diets by the research dietician on the basis of a randomisation schedule provided by the statistician"

Hill 2005 *(Continued)*

		Comment: no further details. Wrote to study author but received no response
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment**: not possible to blind participant mothers as diets were different
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment**: not possible to blind participant mothers as diets were different
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: participant enrolment/study progress diagram included in paper. Accounted for all participants
Selective reporting (reporting bias)	High risk	**Comment**: no specific mention or reporting of adverse effects. No response received from study author
Other bias	High risk	**Comment**: funded by Rice Grower's Co-operative, and intervention includes a rice drink and rice bread daily. No further details of involvement and no response received from study author

Jakobsson 2000

Methods	Randomised, cross-over-style, baseline-control trial with 2 treatment groups
Participants	**Sample size**: 22 enrolled infants (7 dropped out – 3 from CH1 and 4 from CH2) **Setting**: outpatient clinic of a hospital. Recruited from well-baby clinics in Malmö, Sweden **Sex**: 7 boys (47%) 8 girls (53%) **Mean age**: not reported (SD not reported, range 2 to 8 weeks) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: 7.36 h/d (SD 1.32) **Feeding**: formula fed (100%) **Birth order**: not reported **Inclusion criteria**: severe colic: "crying for many times per day for at least 4 days in a week, and continuing for one week or more with each episode lasting 30 minutes to 2 hours, totaling > 3 hours per day" (quote). Symptoms not resolved after parenting and feeding advice given to mother. Anti-spasmodic and anti-cholinergic drugs to manage the colic may have been tried prior to enrolment **Exclusion criteria**: spontaneous resolution, removed for vomiting, refused to follow the protocol, families must not have previously used hydrolysed formula for their babies
Interventions	**Intervention (n = 22)**: Alimentum hydrolysate formula with iron (Abbott Laboratories, CH1) or Nutramigen hydrolysate formula with iron (Mead Johnson Nutritionals, CH2) **Control (n = 22)**: baseline infant's standard formula

Jakobsson 2000 *(Continued)*

	Duration: 1 week
Outcomes	Parents recorded daily crying time in h/d, crying intensity, and other colicky behaviour (summarised as a percentage of the days a particular feature was observed). Formula intake and stool consistency also recorded
Notes	**Study start and end dates**: not reported **COIs**: not reported **Funding source**: not reported **Adverse effects**: none reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "at enrolment, infants were randomised to one of two feeding sequences: CH1 for a week then CH2, or CH2 for a week then CH1 in crossover style"
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author but no received response
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment**: no details. Wrote to study author but received no response
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment**: no details. Wrote to study author but received no response
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment**: some data missing after death of one of the investigators
Selective reporting (reporting bias)	Low risk	**Comment**: mention of clear methods and adverse effects no protocol.
Other bias	Low risk	**Comment**: none noted

Kanabar 2001

Methods	Double-blind, randomised, placebo-controlled cross-over trial with 2 treatment groups
Participants	**Sample size**: 53 infants (7 dropped out – groups not clear) **Setting**: Guy & St Thomas Hospital London, UK **Sex**: not reported **Mean age**: not reported (SD not reported, range 3 to 13 weeks). Mothers given trial literature in the recovery room after birth and asked to get in touch if their babies had colic

Kanabar 2001 *(Continued)*

	Mean weight: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: not reported **Birth order**: not reported **Inclusion criteria**: visit from community midwife at home to establish if baby meets trial criteria. Colic according to Wessel criteria adapted to 14 days of symptoms, does not specify that infants were otherwise well, but recruitment was via general population and supervised by a midwife **Exclusion criteria**: changes of address, and a failure to understand the dosage instructions
Interventions	**Intervention (n = not stated)**: Colief lactase drops. For formula-fed babies, 2 drops added to every made-up formula bottle then bottle refrigerated for 4 h before use. For breastfed babies, mother to express 'foremilk' onto a spoon, add 4 drops of lactase, and then give this at the end of a feed (having tested this method of short incubation with small volume of milk *in vitro*, using 15 mL Aptamil – not breast milk) **Control (n = not stated)**: heat inactivated placebo of the lactase obtained from the manufacturer, in identical packaging, delivered in the same way **Duration**: treatment for each feed for 10 days
Outcomes	Parents noted total daily crying time in minutes over 10 days, and breath hydrogen testing done before and after a single feed on day 10 to assess whether treatment produced 45% less crying time
Notes	**Study start and end dates**: not reported **COIs**: Treatment products – both intervention and control – provided by Crosscare Ltd, the manufacturer of Colief, which was being tested in this study **Funding source**: not reported but see COIs directly above **Adverse effects**: none reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "randomly assigned by use of a predetermined computer-generated randomisation schedule, to verum or placebo arm for 10 days"
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: double-blind, identical packaging of intervention and control
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment**: says double-blind but paper does not make clear whether outcome assessors were aware of treatment arm when analysing parents' records. Wrote to study author but received no response
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: paper states that 46 (out of 53) participants were available for "cry time analysis" (quote) and the reasons for non-availability included changes

Kanabar 2001 *(Continued)*

All outcomes		of address and failure to understand dosage instructions. A significant proportion (14/46) were found to be non-compliant with the usage of the lactase or placebo (judged by the amount that was gone from the bottle)
Selective reporting (reporting bias)	Low risk	**Comment**: paper reports on per-protocol and intention-to-treat data but the results from the two cross-over arms are lumped together so meta-analysis not possible Adverse effect data given
Other bias	High risk	**Comment**: this is a cross-over study but the data is lumped together so we could not, as preferred, refer only to data from the first arm of the study. Wrote to study author for separate data but received no response Treatment products – both intervention and control – provided by Crosscare Ltd, the manufacturer of Colief, which was being tested in this study

Kearney 1998

Methods	Randomised, double-blind, cross-over trial with 2 treatment groups
Participants	**Sample size**: 13 infants (0 dropped out) **Setting**: general practices and paediatric clinics in Cork, Ireland **Sex**: 9 boys (69%) 4 girls (31%) **Mean age**: 53.5 days (SD 26.2, range 23 to 113 days) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: formula fed (100%) **Birth order**: not reported **Inclusion criteria**: formula-fed infants with colic symptoms using a modified Wessel's criteria: full force crying for ≥ 3 h/d for ≥ 3 d/week. Their definition did not require crying of 3 weeks or more **Exclusion criteria**: 'otherwise well' (quote)
Interventions	**Intervention (n = not reported)**: lactase (Lactaid) drops; 3 drops added to each feed, which was then refrigerated for 24 h before feeding to the baby **Control (n = not reported)**: placebo supplied by manufacturer for lactase (Lactaid) drops; 3 drops added to each feed, which was then refrigerated for 24 h before feeding to the baby **Duration**: 1 week
Outcomes	Parents asked to keep a diary containing information about baby's crying time, stool habit and details of volumes, strength and type of formula
Notes	**Study start and end dates**: not known **COIs**: none reported **Funding source**: Mediplan and Myplan, who make the lactase product Lactaid, which was used as the intervention

Kearney 1998 *(Continued)*

	Adverse effects: none reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "random permutated blocks of size four to ensure that the numbers of babies assigned to the two treatment orders were fairly even"
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote**: "preparations given in bottles marked week 1 and week 2 to ensure the double blind nature of the trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment**: no details at all. Wrote to study author but received no response
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote**: "13 babies completed the trial" **Comment**: does not say how many began the trial
Selective reporting (reporting bias)	Low risk	**Comment**: results from each cross-over arm are lumped together in the data reports so meta-analysis not possible Adverse effect data given
Other bias	High risk	**Comment**: funded by industry and no response received from study author to confirm level of involvement

Lothe 1987

Methods	Double-blind, cross-over trial with 1 treatment group
Participants	**Sample size**: 65 infants (5 dropped out) **Setting**: children's hospital in Malmö, Sweden **Sex**: 23 boys (38%) 37 girls (62%) **Mean age**: 6.38 weeks (SD 2.50, range 3 to 13) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: predominantly or totally formula-fed infants **Birth order**: not reported **Inclusion criteria**: severe colic (paroxysmal abdominal pain, severe crying for several hours per day especially between 5 pm and 10 pm, abdomen distended by gas, and the wish to suck often). Infants re-

Lothe 1987 *(Continued)*

	ceiving dimeticonum, methylscopolaminum and dicycloverine-chloride with no effect were able to participate. **Exclusion criteria**: urinary infections
Interventions	**Intervention (n = not clear)**: one can of ProSobee (soy protein-based formula) for 1 week **Control (n = not clear)**: Enfamil (standard cows' milk protein-based formula) for 1 week **Duration**: observation period of 1 week followed by a week of either cows' milk protein-based formula or soy protein-based formula. The infants were then swapped onto the other formula and the results of the 2 cross-over arms' were pooled for reporting in the paper
Outcomes	Parents given standardised protocols and asked to record the length of the crying period and any changes in stools and vomit
Notes	**Study start and end dates**: 1980 (start); end date not reported **COIs**: not reported **Funding source**: control and intervention products manufactured and provided free by Mead Johnson **Adverse effects**: not reported **Comments**: formulas were provided and coded by Mead Johnson; any babies still symptomatic on soy formula were then given cows' milk protein hydrolysate formula Nutramigen, also provided by Mead Johnson

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: says double-blind cross-over. Does not say randomised anywhere
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: says double-blind cross-over. Cans were labelled by Mead Johnson
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "at the end of the test period ... the protocols were evaluated and the code was broken"
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment**: 60 participants (out of 65 at outset) completed the trial. No explanation of the other 5
Selective reporting (reporting bias)	High risk	**Comment**: reported on a per-protocol rather than an intention-to-treat basis, no specific adverse effect data given
Other bias	Unclear risk	**Comment**: cans were labelled by Mead Johnson

Lucassen 2000

Methods	Randomised, double-blind, parallel trial with 2 treatment groups
Participants	**Sample size**: 38 infants (5 dropouts: 2 from illness, 2 from non-compliance, and 1 referred because of worsening symptoms – 3 intervention, 2 control) **Setting**: infants recruited from community-based, well-child clinics in 6 regions of an area of Holland with 7500 births annually, co-ordinated by the Academic Hospital of Vrije University, Amsterdam, The Netherlands **Sex**: 19 boys (50%) **Mean age**: 7.7 weeks (SD not reported, range 6.4 to 8.9) intervention; 8.3 weeks (SD not reported, range 6.6 to 10.1) control **Mean weight**: 4.5 kg (4.2 to 4.8) intervention; 4.9 kg (4.3 to 5.6) control **Mean duration of colic (baseline)**: 403 min/day (341 to 466) intervention; 328 min/day (291 to 366) control **Mean crying (baseline)**: 299 min/day (251 to 347) intervention; 267 min/day (226 to 307) control **Feeding**: fully formula fed or fed with mix of breast and formula, but the paper neither specifies how many babies were also receiving breast milk, nor treated the receipt of breast milk as a confounding factor **Birth order**: not reported **Inclusion criteria**: infants with good medical condition on examination by clinic doctor, thriving, formula fed (at least 1 formula feed per day), good feeding technique, < 6 months old, crying > 3 h/d on at least 3 d/week **Exclusion criteria**: history of anaphylaxis to cows' milk, previous trial of hypoallergenic feeding, refusal to give informed consent, communication problems, referred to paediatrician, no crying problem anymore, other illness, other advice from own doctor, refusal to keep diary
Interventions	**Intervention (n = 23)**: Nutricia whey hydrolysate formula **Control (n = 20)**: Nutricia standard formula **Duration**: 1-week study after baseline for one week
Outcomes	Parents instructed on the use of a 24-h diary and questionnaire to assess minutes of crying per 24 h, which included the question, "Do you know which formula your infant has been using this week?" (quote) to test for adequate blinding. Evaluation of results to include proportion of infants who, after the intervention, would no longer meet the inclusion criteria
Notes	**Study start and end dates**: August 1994 (start) to October 1996 (end) **COIs**: Nutricia provided the formula **Funding source**: Praeventie Fonds – the Dutch National Preventative Fund **Adverse effects**: none reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment**: randomised to intervention or control group by SPSS Inc, Chicago

Lucassen 2000 *(Continued)*

Allocation concealment (selection bias)	Low risk	**Comment**: response from study author as follows (quote), "a box containing the formula was sent to each participating centre. Each box contained 16 cans of formula of which 8 contained hypo-allergenic formula and 8 normal formula (of which taste and smell were changed in the direction of hypoallergenic formula). All cans were identical and contained a sticker with a number. Each set of two cans had the same number (so it was impossible to provide one can with hypoallergenic formula and one can with control formula to the same infant). The local centre distributed the cans, two for each infant. The persons at the local centre were completely unaware of the codes. The codes were generated with a random numbers list"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: study author responded. Blinding of parents was made possible by changing the taste and smell of the control formula in the direction of taste and smell of the hypoallergenic formula
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment**: study author responded. Blinding of the parents was made possible by changing the taste and smell of the control formula in the direction of taste and smell of the hypoallergenic formula
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: accounted for all participants
Selective reporting (reporting bias)	Low risk	**Comment**: study author contacted and we were informed that there were no adverse effects
Other bias	Unclear risk	**Comment**: Nutricia provided the formula. Contact from the study author tells us that Nutricia did not play any role except in the provision of the formulas; they were not involved in writing or checking the manuscript

Miller 1990

Methods	Double-blind, cross-over trial with 2 treatment groups
Participants	**Sample size**: 15 (0 dropped out) **Setting**: infants recruited from a family care centre serving the northern suburbs of Sydney, Australia **Sex**: 5 boys (33%) 10 girls (67%) **Mean age**: 6.5 weeks (SD 2.2, range 3 to 9) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: breastfed (100%) **Birth order**: not reported **Inclusion criteria**: total duration of crying and fussing of at least 3 h in 2 consecutive 24-h periods; crying and fussing behaviour not responding to mother-craft skills, and no apparent cause for the crying and fussing **Exclusion criteria**: hydrogen concentration in breath of over 20 ppm

Miller 1990 *(Continued)*

Interventions	**Intervention (n = not reported)**: lactase (Lactaid) in glycerol, 6 drops into baby's mouth within 5 min of commencing feed **Control (n = not reported)**: glycerol with water and caramel, 6 drops into baby's mouth within 5 min of commencing feed **Duration**: 7 days in each treatment arm
Outcomes	Mothers instructed on how to complete a 24-h recording form detailing durations of infant behaviours such as sleeping, being awake and content, crying, fussing and feeding, to determine the mean number of minutes of crying or fussing in 24 h. Also, measurement of H_2 concentrations in pre-and post-prandial breath tests, to determine the effect of yeast lactase on the mean value of each infants' breath hydrogen
Notes	**Study start and end dates**: July 1987 (start) to June 1988 (end) **COIs**: none reported **Funding source**: Sharpe Laboratories, which seemed to have produced the active and placebo preparations, but no details available as to any further extent of their involvement **Adverse effects**: none reported **Comments**: cross-over study but we reported on the first arm only. Based on PhD Thesis by John Miller

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "infants were randomly allocated" **Comment**: we contacted the study author who was unable to confirm how the random list was generated **Quote**: "Dr D Shaw, Principal Consultant, Siromath, Sydney, performed the sample size calculation and I recall that he also provided a randomisation schema for allocation of the treatments to the breast fed, and to the formula-fed infants. I don't remember how these randomisation schema were derived"
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author who was unable to confirm whether this was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: described as double-blind but method not specified. Wrote to study author who responded stating, "The active & placebo enzyme preparations were aseptically filled into plastic squeeze bottles, capped, packed into tamper-proof plain cardboard cartons and labelled with a code by Sharpe Laboratories, Sydney. The packaged preparations were indistinguishable except for the labelled code."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment**: no details. Wrote to study author who responded stating, "The active & placebo enzyme preparations were aseptically filled into plastic squeeze bottles, capped, packed into tamper-proof plain cardboard cartons and labelled with a code by Sharpe Laboratories, Sydney. The packaged preparations were indistinguishable except for the labelled code."
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: 15 entered the study, but only 12 completed the study and no reasons for non-completion are provided in the paper. We contacted the study author who replied stating, "Of these infants, 2 'dropped out' – 1 on active treatment, the other on placebo. In the former case, active treatment was discontinued after 48 hours because the parents considered the treatment wors-

Miller 1990 *(Continued)*

		ened crying and fussing behaviour. In the latter case, the mother stopped using the placebo after 4 days because of lack of effect. One infant was withdrawn from the study. In this case, the mother was admitted to hospital with a breast abscess. The infant was temporarily weaned. However, at the mother's request, active treatment was continued."
Selective reporting (reporting bias)	Low risk	**Comment**: results are based on per protocol, not intention-to-treat, but all major outcomes are reported, with adverse effect data given by study author
Other bias	Unclear risk	**Comment**: designed as cross-over trial but we reported on the first arm only. Sharpe Laboratories were the study sponsor and seemed to have produced the active and placebo preparations but no details were available as to any further extent of their involvement. The study author confirmed no involvement.

Oggero 1994

Methods	Randomised controlled trial with 3 treatment groups
Participants	**Sample size**: 120 infants (0 dropped out) **Setting**: Department of Pediatrics at the University of Turin, Children Hospital Regina Margherita, Turin, Italy **Sex**: not reported **Mean age**: 6.2 weeks (SD not reported, range 3-12 weeks) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: formula fed (n = 89), and breastfed (n = 31). No mention of any of the babies being mixed fed **Birth order**: not reported **Inclusion criteria**: infants aged 3-12 weeks suffering from severe colic, symptoms lasting for at least 2 weeks, presence of inconsolable crying, closed fists and meteorism, presence of sleep disorders, crying for more than a total of 3 h/d, no response to common consolation procedures (pacifier, rocking, dull continuous background noise, hot water bottle on abdomen) **Exclusion criteria**: known organic causes of abdominal pain
Interventions	**Intervention (n = 60)**: hypoallergenic dietary regimen. Breastfed babies' mothers were given a diet containing no milk, eggs or fish; formula-fed babies were given soy milk (If symptoms continued the symptomatic, formula-fed babies were moved onto Nutramigen for 15 days – these data are not included in our analyses) **Control (n = 60)**: gastrointestinal antispastic drugs. All infants given dicyclomine hydrocholoride (3 mg/kg/day divided into 3 doses per day), and no dietary modifications were made **Duration**: 15 days
Outcomes	Parents asked to note the beginning and end of unexplained crying spells and to note the beginning and end of unexplained periods of fussiness or irritability. The evaluation of treatment results based on this information gathered by parents and written in a diary
Notes	**Study start and end dates**: not reported in the text. October 1991 (start) to January 1993 (end)

Oggero 1994 *(Continued)*

COIs: none reported

Funding source: none reported

Adverse effects: none reported

Comments: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "randomly divided"
Allocation concealment (selection bias)	High risk	**Comment**: participants were randomly assigned to the different groups but the type of treatment was known (not blinded)
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment**: not possible to blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment**: not a blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: accounted for all participants
Selective reporting (reporting bias)	High risk	**Comment**: study authors reported results for all outcomes declared in the Methods section, except adverse effects which are not reported.
Other bias	Low risk	**Comment**: no significant differences between groups at baseline were reported

Savino 2005

Methods	Randomised, double-blind, placebo-controlled trial with 2 treatment groups
Participants	**Sample size**: 93 colicky infants (5 dropped out (2 = intervention, 3 = control); 2 did not come to the second visit, 3 were excluded because of fever. Nobody withdrew because of problems related to the trial and therefore the study population may be considered homogeneous) **Setting**: recruited from patients seen at the Department of Pediatrics, Regina Margherita Children's Hospital, University of Turin, Italy **Mean age**: 4.2 weeks (SD 1.4, range not reported) intervention; 4.4 weeks (SD 1.6, range not reported) control **Sex**: 41 (46.6%) boys (18 intervention, 23 control); 47 (53.4%) girls (23 intervention, 24 control) **Mean weight**: 3420 g (SD 390) intervention; 3510 g (SD 330) control **Mean duration of colic**: not reported **Mean crying**: 201.2 min (SD 18.3) intervention; 198.7 min (SD 16.9) control

Savino 2005 *(Continued)*

	Feeding: not specified **Birth order**: not specified **Inclusion criteria**: colic according to Wessel criteria, breastfed, healthy infants with regular growth, 21 to 60 days old, born at term (gestational age 38 to 42 weeks), birth weight between 2500 g and 4000 g, no clinical evidence of gastroenterological disease, and Apgar (appearance, pulse, grimace, activity, respiration) score > 7 at 5 min after birth **Exclusion criteria**: infants receiving any medication, such as antibiotics or probiotics, which could affect abdominal symptoms
Interventions	**Intervention 1 (n = 41)**: phytotherapeutic agent (extracts of *Foeniculum vulgare* (fennel), *Matricaria recutita* (chamomile), and *Melissa officinalis* (lemon balm)). Each dose of herbal agent consisted of 1 bottle, with tank cap, containing *Foeniculum vulgare miller var. dulce* (164.29 mg), *Matricaria recutita L.* (177.69 mg), *Melissa officinalis L.* (96.89 mg), vitamin B1 (0.85 mg), calcium pantothenate (3.24 mg), vitamin B6 (1.20 mg), maltodextrin (dose not specified) and syloid 244 FP (dose not specified) (ColiMil, Milte-Milan, Italy). At the administered dosage, the herbal agent provided *Foeniculum vulgare miller var. dulce* 65.71 mg/kg/d, *Matricaria recutita L.* 71.10 mg/kg/d, and *Melissa officinalis L.* 38.75 mg/kg/d **Control (n = 47)**: placebo looking like the phytotherapeutic agent with regard to colour, smell, taste and package, but containing only vitamins. Each dose of placebo consisted of 1 identical bottle, with tank cap, containing water obtained by inverted osmosis, fructose, pineapple flavour, citric acid and sorbate potassium. **Administration**: both herbal agent and placebo were administered twice a day at 5 pm and 8 pm, some minutes before feeding, at a dosage of 2 ml/kg/d. Infants had to take treatment consecutively for 7 days **Duration**: 21 days
Outcomes	Parents wrote a daily, structured diary, recording (1) the start of crying time – when the medication was administered, (2) the end of crying time, and (3) any side effects (vomiting, sleepiness, restlessness, appetite, cutaneous reactions, constipation, diarrhoea) they observed for the 7 days of therapy and until day 21 from enrolment. Before starting treatment, parents were invited to record data on daily crying time for 3 days (days 0, 1, and 2). At days 1 and 7, infants were seen in the department, and parents gave the diary to researchers. At day 21, after baseline, mothers were asked to complete a questionnaire about crying time during the observation period. To ensure that all parents noted crying time in a uniform way, and to ensure that infants were given medication correctly, a researcher was always available by phone to help parents. Therapy was considered effective if crying time was reduced by ≥ 50% per day; responders were infants who showed such a reduction in crying time
Notes	**Study start and end dates**: March 2001 (start) to March 2003 (end) **COIs**: none reported **Funding source**: funded, in part, by Milte who provided the study products but had no other role in the study; they were not involved in writing or checking the manuscript **Adverse effects**: no adverse effects **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment**: this was performed by computer
Allocation concealment (selection bias)	Low risk	**Comment**: conducted by a statistician not involved with the study

Savino 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: placebo looked like the phytotherapeutic agent with regard to colour, smell, taste and packaging **Quote**: "Neither doctors nor parents knew whether the infants received treatment or not"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote**: "Neither doctors nor parents knew whether the infants received treatment or not"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: 5 infants (2 from the intervention group and 3 from the placebo group) dropped out: 2 did not come to the second visit, and 3 were excluded because of fever. Nobody withdrew because of problems related to the trial.
Selective reporting (reporting bias)	Low risk	**Comment**: study authors reported results for all outcomes declared in the Methods section
Other bias	Low risk	**Comment**: no significant differences between groups at baseline were reported

Savino 2006

Methods	Prospective, randomised controlled trial with 2 treatment groups
Participants	**Sample size**: 267 recruited (68 withdrawn (34 intervention, 34 control); 45 (20 intervention, 25 control) did not meet inclusion criteria by the time the study began, and 23 (14 intervention, 9 control) excluded during the study due to missing data) **Setting**: 78 general paediatricians and the Department of Pediatrics based at the University of Turin, Children Hospital Regina Margherita, Turin, Italy **Sex**: 50 (52.1%) boys intervention, 49 (47.6%) boys control; 47.9% girls intervention, 52.4% girls control **Mean age**: 1.39 months (SD 0.84, range not reported) intervention; 1.29 months (SD 0.77, range not reported) control; less than 4 months at age of entry into study **Mean weight**: not reported **Mean duration of colic (baseline)**: 5.99 colic episodes per day (SD 1.84) intervention, 5.41 colic episodes per day (SD 1.88) control **Mean crying (baseline)**: not reported **Feeding**: formula fed (100%) **Birth order**: not reported **Inclusion criteria**: infants aged less than 4 months, with infantile colic according to Wessel definition, gestational age between 37 and 42 weeks, normal birth weight (> 2500 g), regular weight gain (more than 150 g/week) and normal physical examination **Exclusion criteria**: neonatal problems, consumption of any kind of medication during the week before the beginning of the study and during the study period
Interventions	**Intervention (n = 130)**: Numic oOmneo Comfort (100% whey protein, low lactose, contains GOS/FOS) **Control (n = 137)**: Numico Nutrilon Standard 1 formula plus simethicone (rationale being that simethicone* is as effective as placebo (Lucassen 1998), so used as placebo) **Duration**: 2 weeks

Savino 2006 *(Continued)*

	*Simethicone is an anti-foaming agent designed to reduce the surface tension of bubbles of gas trapped in liquid, so they group together and can be passed more easily. As such, this is not a dietary modification and its addition to the standard formula was intended, in this case, to assess the superiority of the intervention formula, which contained oligosaccharides thought to improve the balance of the infant's microbiota, over the common recommendation to administer simethicone to infants with colicky symptoms, alongside their regular milk. The oligosaccharide blend used in this study formula was reported as being 90% galacto-oligosaccharide and 10% fructo-oligosaccharide (known as GOS/FOS), and the formula also had a 100% whey base rather than standard formula's 60:40 whey:casein ratio, and a lower lactose level than standard formula (with additional maltodextrin and starch to thicken the milk), in addition to the cows milk proteins having been partially hydrolysed. This study was a larger scale comparison with 103 of the infants who completed the trial randomised to the control with standard casein-based formula plus simethicone, and 96 randomised to the intervention of a partially hydrolysed, lower lactose, whey-based formula with starches, and supplemented with oligosaccharide
Outcomes	Questionnaire given to parents to monitor symptoms, frequency and feeding volume. On days 1, 7 and 14, infants examined by paediatricians. Feeding frequency and feeding volume was decided by the family and not by the study protocol. The number of significant colic episodes (over 40 min in duration) was recorded by parents daily. Study measured number of colic episodes per day (multivariate analysis between intervention or control pairs adjusted for variables)
Notes	**Study start and end dates**: August 2002 (start) to January 2003 (end) **COIs**: none reported **Funding source**: Numico, Italy, who provided the intervention formula **Adverse effects**: not reported, but we contacted the author, who is also an author on this review, who confirmed these were recorded and none were experienced **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment**: effective randomisation
Allocation concealment (selection bias)	Low risk	**Comment**: sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment**: not possible because of simethicone
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment**: blinding of outcome assessment performed by statistician
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: 68/267 excluded at the end of the trial for non-adherence to intervention or control, or because lost to follow-up – see above under 'Participants'. Clarified by study author
Selective reporting (reporting bias)	Low risk	**Comment**: accounted for all participants. Study authors confirmed no adverse effects experienced
Other bias	Unclear risk	**Comment**: study supported by funds from Numico, Italy. They were not involved in writing or checking the manuscript.

Taubman 1988

Methods	Randomised controlled trial with 2 treatment groups. For our purposes, we have labelled 'maternal dairy-free diet' and 'parental counselling plus usual diet', as 'intervention' and 'control' respectively.
Participants	**Sample size**: 11 (1 dropout) in group 1; 10 (0 dropouts) in group 2 **Setting**: private practice and the gastroenterology clinic at the Children's Hospital of Philadelphia, Pennsylvania, USA **Sex**: not reported **Mean age**: 5.4 weeks (SD 2.2, range not reported) intervention; 6.5 weeks (SD 1.8, range not reported) control **Mean weight**: not reported **Mean duration of colic (baseline)**: 3.75 weeks (SD 5.8) intervention; 4.85 weeks (SD 4.12) control **Mean crying (baseline)**: 3.21 h/d (SD 1.10) intervention; 3.19 h/d (SD 0.69) control **Feeding**: not reported **Birth order**: 3 first born in each group (30%) **Inclusion criteria**: infants crying for more than 2 h/d, younger than 3 months of age, normal growth and development, normal physical findings, no history of diarrhoea or vomiting, and receiving enough milk **Exclusion criteria**: babies already receiving Nutramigen hydrolysed milk or breastfed babies whose mothers are already eating dairy-free
Interventions	**Intervention* (n = 11)**: maternal dairy-free diet if baby breastfed, or Nutramigen hydrolysed casein formula if baby formula fed **Control (n = 10)**: parental counselling plus usual diet **Duration**: 9 days duration in each treatment arm of study *The intervention group went on to have counselling along with return to usual diet. This is not included in our analysis as is the second treatment arm, and we only used data from first treatment arm.
Outcomes	Parents kept a diary of the infants behaviour, in the prescribed manner, during both phases of the study and returned them to the investigator every 2 or 3 days
Notes	**Study start and end dates**: not reported **COIs**: none reported, but see funding source directly below **Funding source**: funded, in part, by Mead Johnson, who provided the intervention formula **Adverse effects**: not recorded **Comments**: this was a 2-phased, randomised study with 11 infants in the counselling group (group 1) and 10 in the 'dairy and soy free' group (group 2), although the first group lost 1 participant from the study in the first few days and did not include that infant's data in the results. 3 infants in the counselling group were breastfed and 4 infants in the dairy and soy free group were breastfed. This study was designed to show the effectiveness of counselling by using dietary changes as a comparison.

Risk of bias

Bias	Authors' judgement	Support for judgement

Taubman 1988 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Comment**: effective randomisation. Investigator had no knowledge of the allocation until after consent was given
Allocation concealment (selection bias)	High risk	**Comment**: no details
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment**: not possible given the nature of the trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment**: no details. Wrote to study author but received no response
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment**: accounted for all participants, though paper reports per protocol, not intention-to-treat, results after one participant dropped out of the control group
Selective reporting (reporting bias)	High risk	**Comment**: paper reports per protocol, not intention-to-treat, results after one participant dropped out of the control group. Adverse effects not reported
Other bias	High risk	**Comment**: funded, in part, by Mead Johnson, who provided the intervention formula

Treem 1991

Methods	Double-blind, randomised, 2-period, cross-over trial with 2 treatment groups
Participants	**Sample size**: 33 infants (6 dropped out – sequence group not clear) **Setting**: paediatricians in the greater Hartford community, Connecticut, USA **Sex**: 13 boys (48%) 14 girls (52%) **Mean age**: 34 days (SD not reported, range 10 to 54) **Mean weight**: not reported **Mean duration of colic (baseline)**: not reported **Mean crying (baseline)**: not reported **Feeding**: formula fed (100%) **Birth order**: 15 first born **Inclusion criteria**: crying as if in pain, crying suddenly, crying continuously for more than 15 min at a time, and difficult or impossible to console during these crying spells, with colic defined as more than 3 h crying or fussing per day on at least 3 days out of 6 successive days, birth weight > 2500 g, normal gestational age, absence of neonatal problems, normal weight gain (> 150 g/week), normal physical examination **Exclusion criteria**: infants on medications during the first week before or during the study
Interventions	**Intervention (n = 12)**: Isomil with soy polysaccharide added to increase dietary fibre (mean values 14.1 g dietary fibre per litre) **Control (n = 15)**: Isomil with nothing added (mean values 3.1 g dietary fibre per litre)

Treem 1991 *(Continued)*

	Duration: baseline for 1 week before beginning study. Cross-over study, including 3-day washout between 2 × 9-day-long arms of study. Patients seen 5 times during the study: at the beginning of the baseline period, at each of the 2 × 9-day study periods, at the end of the last 9-day period, and at the 30- to 35-day follow-up period. Parents also contacted by telephone at least once during each of the 2 × 9-day study periods
Outcomes	Daily behaviour, feeding, and stool diaries completed for 27 days. At the end of this time, parents asked to indicate during which study period the symptoms of colic were most alleviated and whether the infant's symptoms were alleviated during one of the study periods more than during any time before the study. We did not include these data in our analysis as we were looking only at the first arm. Results for crying and fussing in min per 24 h, but aggregated cross-over data
Notes	**Study start and end dates** not reported **COIs**: none reported **Funding source**: supported by grants from Ross Laboratories **Adverse effects**: not reported **Comments**: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment**: randomised
Allocation concealment (selection bias)	High risk	**Comment**: no details. Wrote to study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment**: double-blind and disguised
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment**: no details. Wrote to study author but received no response
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment**: accounted for all participants
Selective reporting (reporting bias)	High risk	**Comment**: accounted for all participants, adverse effects not reported
Other bias	High risk	**Comment**: supported by grants from Ross Laboratories who make Isomil. No further details of involvement were available from the study author

COIs: conflicts of interest; **GP**: general practitioner; **HV**: health visitor; **SD**: standard deviation; **SPSS**: Statistical Package for the Social Sciences.

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

Study	Reason for exclusion
Arikan 2008	Appears to be randomised, but study authors state that in order to prevent discontinuation of breastfeeding, only participants who were formula fed went into the group receiving hydrolysed formula, so, in fact, not random
Barr 1991	Not suffering with colic on entry to study
Bellaiche 2018	Not an RCT
Berseth 2009	No definition of colic: "parent-identified as very fussy or extremely fussy in the baseline tolerance evaluation" (quote)
Buchanan 1998	Letter to Editor of *BMJ*
Campeotto 2011	Not suffering with colic on entry to study
Dupont 2010	Using probiotics to treat so not dietary modification
Evans 1981	Not an RCT – no control
Gerrard 1984	Narative review only
Giovannini 2014	Not suffering with colic on entry to study
Iacono 1991	Not an RCT – no control
Iacovou 2018	Recruited infants did not match infantile colic criteria reported in their own Methods
Imanieh 2004	Study looking for skin prick test as predictor of cows' milk protein allergy in colicky infants
Infante 2011	Not colic by our definition: only 35% (7 out of 20) infants included in analysis cried for more than 3 h/d at baseline
Jakobsson 1983	Not an RCT or quasi-RCT
Koonce 2011	Narrative review only
Laws 1991	Letter to Editor of *Journal of Pediatrics*
Liebman 1981	Not an RCT or quasi-RCT
Nocerino 2012	Conference abstract; not randomised
Pärtty 2015	Using probiotics to treat so not dietary modification
Rozé 2012	Not suffering with colic on entry to study
Sargsyan 2006	Letter to Editor of *European Journal of Pediatrics*
Savilahti 1989	Not an RCT or quasi-RCT
Savino 2003	Not colic by our definition
Sherman 2015	Not suffering with colic on entry to study
Vandenplas 2017	Not suffering with colic on entry to study

Study	Reason for exclusion
Vivatvakin 2010	Not suffering with colic on entry to study
Xinias 2017	Not an RCT – consecutive entry

RCT: randomised controlled trial.

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

NCT01721850

Trial name or title	**Title**: Evaluation of safety and efficacy of new infant formula in infantile colic (Coco) **Official title**: Evaluation of the safety and efficacy of new infant formula and its effects on the gastrointestinal tolerance (crying time) in infantile colic: a double-blind, randomised, controlled intervention study
Methods	Double-blind, randomised-controlled intervention study
Participants	**Inclusion criteria** 1. Healthy, term infants 2. Participants appropriate for gestational age, between 35 and 41 weeks 3. Participants between 15 and 60 days old 4. Participants with birth weight between 2500 g and 4200 g, and with regular weight gain (≥ 150 g/week) 5. Diagnosis of infantile colic according to modified Wessel criteria (crying episodes lasting ≥ 3 h/d and occurring ≥ 3 d/week for at least 1 week) 6. Participants exclusively formula-fed at study entrance 7. Day care of the child only by mother or father or both 8. Provide written informed consent in accordance with legal requirement **Exclusion criteria** 1. Neonatal problems (respiratory distress, asphyxia, Hypoglycaemia, sepsis, necrotising enterocolitis) 2. Clinical evidence of chronic illness or gastrointestinal disorders (gastroesophageal reflux, gastroenteritis) 3. Assumption of any kind of medication (except vitamin D, vitamin K and fluoride prophylaxis) during the week before the beginning of the study and during the study period 4. Participants receiving formula for special medical purposes 5. Exclusively breastfed infants 6. Feeding of supplemental probiotics or prebiotics (or both) 2 weeks prior to inclusion 7. Allergic diseases (manifest atopic dermatitis, cows' milk allergy) 8. Participation in any other clinical intervention
Interventions	Parallel assignment with 3 arms: 1. control formula (standard formula) 2. intervention formula 1 (infant formula with hydrolysed protein (type I) and pre- and probiotics 3. intervention formula 2 (infant formula with hydrolysed protein (type II) and pre- and probiotics
Outcomes	**Primary outcome** 1. Daily total crying time (time frame: 28 days); evaluation of the difference in the average reduction of daily crying time after 28 days of intervention between the intervention and control groups

NCT01721850 *(Continued)*

	Secondary outcomes 1. Growth parameters (time frame: 90 days); determination of body weight, length, head circumference 2. Tolerance evaluated by stool characteristics, gastrointestinal disorders and side effects (time frame: 28 days); stool characteristics: frequency, consistency and colour; gastrointestinal disorders: regurgitation, obstipation; side effects: vomiting, diarrhoea, skin reactions 3. Formula intake (time frame: 28 days); evaluation of average daily drinking amount and formula acceptance 4. Intestinal microbiota (time frame: 0 to 28 days); evaluation of changes in the composition of the intestinal microbiota (lactobacilli, bifidobacteria, coliforms) after intervention
Starting date	December 2011
Contact information	**Name**: Christina Hecht **Email**: Christina.hecht@hipp.de **Telephone**: 00498441757855
Notes	**Status**: recruiting **Funding source**: HiPP GmbH & Co. Vertrieb KG

NCT02813772

Trial name or title	**Title**: Efficacy of a partially hydrolyzed formula, containing *Lactobacillus reuteri*, for infant colic **Official title**: Efficacy of a partially hydrolyzed formula, containing*Lactobacillus reuteri*, for infant colic: a double blind, randomised-controlled trial
Methods	Double-blind, randomised controlled trial
Participants	**Inclusion criteria** 1. Full-term infants (≥ 37 weeks gestation at birth) 2. Exclusively formula-fed infants at time of enrolment 3. Infants suffering from infantile colic according to Rome III criteria 4. Age < 4 months of life 5. 5-min Apgar (appearance, pulse, grimace, activity, respiration) score ≥ 7 6. Birth weight ≥ 2500 g **Exclusion criteria** 1. Consumption of formula containing probiotics, partially hydrolysed formula or with reduced lactose content at time of enrolment 2. Major medical problem or acute illness, including gastroesophageal reflux, cows' milk protein allergy 3. History of antibiotic treatment before or during the study 4. History of probiotic or *L reuteri* supplementation 5. History of any allergies to any of the ingredients in the probiotic *L reuteri* 6. Concurrent participation in another clinical trial 7. Birth weight < 2500 g 8. Failed to thrive 9. Breastfed infants

NCT02813772 *(Continued)*

	10.NAN infant formula (to avoid the formula switch effect)
Interventions	Parallel assignment: a partially hydrolysed formula with reduced lactose content and *L reuteri* versus a standard formula
Outcomes	**Primary outcome** 1. Whether the administration of a partially hydrolysed formula with reduced lactose content and *L reuteri* is beneficial in infantile colic in reducing the infant crying duration (time frame: 7, 14, 21, 28 days, 2 and 3 months); infant crying duration (min/d) at 7, 14, 21, 28 days, 2 and 3 months postintervention **Secondary outcomes** 1. Whether the administration of a partially hydrolysed formula with reduced lactose content and *L reuteri* is beneficial in infantile colic in reducing the infant crying duration (time frame: 28 days); percentage of responders at 28 days postintervention. A response to the treatment will be defined as 50% of reduction of infant crying. 2. Whether the administration of a partially hydrolysed formula with reduced lactose content and *L reuteri* is beneficial in infantile colic in increasing infant sleep (time frame: 7, 14, 21, 28 days, 2 and 3 months); longer infant sleep duration at 7, 14, 21, 28 days, 2 and 3 months postintervention 3. The effect of a partially hydrolysed formula on quality of life of the enrolled patients (time frame: 3 months); reduction of mean scores of a standardised measure for children's quality of life 4. The effect of a partially hydrolysed formula on quality of life of parents (time frame: 3 months); reduction of mean scores of a standardised measure for parents' quality of life 5. The effect of this infant formula enriched with *L reuteri* on faecal microbiome of colicky infants (time frame: 2 months); changes in gut microbiome 6. Changes in stool frequency and consistency (time frame: 28 days); changes in stool frequency and consistency 7. Parental perception of colic severity (visual analog scale, 0 to 10) (time frame: 28 days); parental perception of colic severity (visual analog scale, 0 to 10) 8. Parental perception of sleep quality (visual analog scale, 0 to 10) (time frame: 28 days); parental perception of sleep quality (visual analog scale, 0 to 10)
Starting date	November 2015
Contact information	**Name**: Annamaria Staiano **Email**: staiano@unina.it **Telephone**: none provided
Notes	**Status**: recruiting **Funding source**: Federico II University

NCT03329222

Trial name or title	**Title**: An infant formula trial on dietary management of infantile colic **Official title**: A randomised, double-blind, controlled, multi-centre study to assess the efficacy of an infant formula in the dietary management of infantile colic
Methods	Double-blind, randomised controlled trial
Participants	**Inclusion criteria** 1. Infants aged 21-56 days (both inclusive)

NCT03329222 *(Continued)*

2. Gestation age 37-42 weeks
3. Normal birth weight for gestational age and gender
4. 5-min Apgar (appearance, pulse, grimace, activity, respiration) score >7
5. Diagnosed with infantile colic
6. Fully formula fed for at least 7 days before randomisation
7. Written informed consent from the parent or legal representative (or both)

Exclusion criteria

1. Any plausible cause of inconsolable crying as judged by the investigator
2. Presence of non-functional vomiting or failure to thrive
3. Presence of any congenital defects in the gastrointestinal system or other defects preventing oral nutrition
4. Combination of congenital condition or previous or current illness/infection and (or) medication use that could interfere with the main study outcomes
5. Known cows' milk protein allergy, lactose intolerance or galactosaemia, including presence of any allergic manifestations
6. Received any special formula (e.g. lactose free, hydrolysed protein)
7. Received any of the following products/medication within 7 days before randomisation: probiotics, systemic antibiotics, prokinetics, proton pump inhibitors
8. Twins or triplets or other infant(s) < 6 months of age living in the same household
9. Incapability of the parent(s) to comply with the study protocol or investigator's uncertainty about the willingness or ability of the participant to comply with protocol requirements
10. Current participation in another clinical study involving investigational or marketed products

Interventions	An infant formula that contains specific hydrolysed proteins with a fat-blend, prebiotic mixture, starch and reduced lactose versus standard cows' milk with prebiotic mixture
Outcomes	**Primary outcome** 1. Daily inconsolable crying time using data recorded on participant's diaries (time frame: 6 weeks); daily inconsolable crying time over 6 weeks **Secondary outcome** 1. Daily crying time using data recorded on participant's diaries (time frame: 6 weeks); daily crying time over 6 weeks of intervention 2. Daily fussing time using data recorded on participant's diaries (time frame: 6 weeks); daily fussing time over 6 weeks of intervention 3. Daily inconsolable fussing time using data recorded on participant's diaries (time frame: 6 weeks); daily inconsolable fussing time over 6 weeks of intervention 4. Daily stool frequency using data recorded on participant's diaries (time frame: 6 weeks); daily stool frequency over 6 weeks of intervention 5. Daily stool consistency using data recorded on participant's diaries (time frame = 6 weeks); daily stool consistency over 6 weeks of intervention 6. The frequency of participants' gastrointestinal symptoms of digestion in the 7-day period prior to the visit using the Infant Gastrointestinal Symptoms questionnaire (time frame: 6 weeks); gastrointestinal symptoms using the Infant Gastrointestinal Symptoms Questionnaire during the 6-week intervention period 7. The intensity of participants' gastrointestinal symptoms of digestion in the 7-day period prior to the visit using the Infant Gastrointestinal Symptoms Questionnaire (time frame: 6 weeks); gastrointestinal symptoms using the Infant Gastrointestinal Symptoms Questionnaire during the 6-week intervention period
Starting date	27 October 2017
Contact information	**Name**: Wan Wen Tee; Anneke Ravensbergen

NCT03329222 *(Continued)*	**Email**: wanwen.tee@danone.com; anneke.ravensbergen@danone.com **Telephone**: +65 68309466; +65 6830 9419
Notes	**Status**: recruiting **Funding source**: Danone Asia Pacific Holdings Pte, Ltd

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library

#1[mh Colic]
#2colic*
#3((stomach or abdominal or abdomen*) near/3 (spasm* or pain* or cramp*))
#4((gastric or gastro*) near/3 (spasm* or pain* or cramp*))
#5[mh Crying]
#6(cry or crying or cries)
#7{or #1-#6}
#8[mh Infant]
#9(baby or babies or child* or infant* or newborn* or neonate*)
#10{or #8-#9}
#11[mh Milk]
#12[mh "Milk, Human"]
#13[mh "Breast Feeding"]
#14(breastfeed* or "breast feed*" or breastfed or "breast fed" or breastmilk* or "breast milk*" or milk*)
#15[mh ^Hypersensitivity]
#16[mh "Food Hypersensitivity"]
#17[mh ^Allergens]
#18[mh "Lactose Intolerance"]
#19(allerg* or hypoallerg* or hypo next allerg* or hyperallerg* or hyper next allerg* or hypersensitiv* or hyper next sensitiv* or intoleran* or non next allerg* or nonallerg* or sensitiv*)
#20[mh "Infant Food"]
#21(formula* or bottle next fed* or bottlefed* or bottlefeed* or bottle next feed*)
#22[mh Hydrolysis]
#23(hydrolys* or hydrolyz*)
#24[mh Prebiotics]
#25[mh ^"Amino acids"] 1
#26(amino next acid* or aminoacid* or casein* or fibre* or fiber* or prebiotic* or pre next biotic* or soy* or whey*)
#27[mh "Dietary Proteins"]
#28[mh "diet therapy"/FS]
#29diet*
#30[mh "Dairy Products"]
#31[mh Fishes]
#32[mh Eggs]
#33[mh Gluten]
#34[mh Nuts]
#35(cheese* or dairy or egg* or fish* or gluten* or wheat* or nut* or peanut* or lactose* or yogurt* or yoghurt*)
#36{or #11-#35}
#37#7 and #10 and #36 in Trials

MEDLINE Ovid

1 Colic/
2 colic$.tw.
3 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw.
4 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw.

5 crying/
6 (cry or crying or cries).tw.
7 or/1-6
8 exp Infant/
9 (baby or babies or child$ or infant$ or newborn$ or neonate$).tw.
10 8 or 9
11 7 and 10
12 Milk/
13 Milk, Human/
14 Breast Feeding/
15 (breastfe?d$ or breast fe?d$ or breastmilk$ or breast-milk$ or milk$).tw.
16 Hypersensitivity/
17 exp Food Hypersensitivity/
18 Allergens/
19 Lactose Intolerance/
20 (allerg$ or hypoallerg$ or hypo-allerg$ or hyperallerg$ or hyper-allerg$ or hypersensitiv$ or hyper-sensitiv$ or intoleran$ or non-allerg $ or nonallerg$ or sensitiv$).tw.
21 exp Infant Food/
22 (formula$ or bottle fed$ or bottlefed$ or bottlefeed$ or bottle feed$).tw.
23 Hydrolysis/
24 (hydrolys$ or hydrolyz$).tw.
25 Prebiotics/
26 Amino acids/)
27 (amino acid$ or aminoacid$ or casein$ or fibre$ or fiber$ or prebiotic$ or pre-biotic$ or soy$ or whey$).tw.
28 exp Dietary Proteins/
29 diet therapy.fs.
30 diet$.tw.
31 exp Dairy Products/
32 exp Eggs/
33 Fishes/
34 Gluten/
35 Nuts/
36 (cheese$ or dairy or egg$ or fish$ or gluten$ or wheat$ or nut$ or peanut$ or lactose$ or yog?urt$).tw.
37 or/12-36
38 11 and 37
39 randomized controlled trial.pt.
40 controlled clinical trial.pt.
41 randomi#ed.ab.
42 placebo$.ab.
43 drug therapy.fs.
44 randomly.ab.
45 trial.ab.
46 groups.ab.
47 or/39-46
48 exp Animals/ not Humans.sh.
49 47 not 48
50 38 and 49

MEDLINE In-Process & Other Non-Indexed Citations Ovid

1 colic$.mp.
2 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).mp.
3 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).mp.
4 (cry or crying or cries).mp.
5 or/1-4
6 (baby or babies or child$ or infant$ or newborn$ or neonat$).mp.
7 5 and 6
8 (breastfe?d$ or breast fe?d$ or breastmilk$ or breast-milk$ or milk$).mp.
9 (allerg$ or hypoallerg$ or hypo-allerg$ or hyperallerg$ or hyper-allerg$ or hypersensitiv$ or hyper-sensitiv$ or intoleran$ or non-allerg $ or nonallerg$ or sensitiv$).mp.
10 (formula$ or bottle fed$ or bottlefed$ or bottlefeed$ or bottle feed$).mp.
11 (hydrolys$ or hydrolyz$).mp.

12 (amino acid$ or aminoacid$ or casein$ or fibre$ or fiber$ or prebiotic$ or pre biotic$ or soy$ or whey$).mp.
13 diet$.mp.
14 (cheese$ or dairy or egg$ or fish$ or gluten$ or wheat$ or nut$ or peanut$ or lactose$ or yog?urt$).mp.
15 or/8-14
16 7 and 15

MEDLINE EPub Ahead of Print Ovid

1 colic$.mp.
2 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).mp.
3 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).mp.
4 (cry or crying or cries).mp.
5 or/1-4
6 (baby or babies or child$ or infant$ or newborn$ or neonat$).mp.
7 5 and 6
8 (breastfe?d$ or breast fe?d$ or breastmilk$ or breast-milk$ or milk$).mp.
9 (allerg$ or hypoallerg$ or hypo-allerg$ or hyperallerg$ or hyper-allerg$ or hypersensitiv$ or hyper-sensitiv$ or intoleran$ or non-allerg$ or nonallerg$ or sensitiv$).mp.
10 (formula$ or bottle fed$ or bottlefed$ or bottlefeed$ or bottle feed$).mp.
11 (hydrolys$ or hydrolyz$).mp.
12 (amino acid$ or aminoacid$ or casein$ or fibre$ or fiber$ or prebiotic$ or pre biotic$ or soy$ or whey$).mp.
13 diet$.mp.
14 (cheese$ or dairy or egg$ or fish$ or gluten$ or wheat$ or nut$ or peanut$ or lactose$ or yog?urt$).mp.
15 or/8-14
16 7 and 15

Embase Ovid

1 colic/
2 colic$.tw.
3 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw.
4 crying/
5 (cry or crying or cries).tw.
6 or/1-5
7 exp infant/
8 (baby or babies or child$ or infant$ or newborn$ or neonate$).tw.
9 7 or 8
10 6 and 9
11 infantile colic/
12 10 or 11
13 milk/
14 breast milk/
15 breast feeding/
16 (breastfe?d$ or breast fe?d$ or breastmilk$ or breast-milk$ or milk$).tw.
17 hypersensitivity/
18 exp nutritional intolerance/
19 exp allergen/
20 lactose intolerance/
21 (allerg$ or hypoallerg$ or hypo-allerg$ or hyperallerg$ or hyper-allerg$ or hypersensitiv$ or hyper-sensitiv$ or intoleran$ or non-allerg$ or nonallerg$ or sensitiv$).tw.
22 exp baby food/
23 (formula$ or bottle fed$ or bottlefed$ or bottlefeed$ or bottle feed$).tw.
24 hydrolysis/
25 prebiotic agent/
26 amino acid/
27 (amino acid$ or aminoacid$ or casein$ or fibre$ or fiber$ or prebiotic$ or pre-biotic$ or soy$ or whey$).tw.
28 exp dairy product/
29 protein intake/
30 diet$.tw.
31 egg/
32 fish/
33 exp nut/
34 gluten/

35 gluten free diet/
36 (cheese$ or dairy or egg$ or fish$ or gluten$ or wheat$ or nut$ or peanut$ or lactose$ or yog?urt$).tw.
37 or/13-36
38 12 and 37
39 Randomized controlled trial/
40 controlled clinical trial/
41 Single blind procedure/
42 Double blind procedure/
43 triple blind procedure/
44 Crossover procedure/
45 (crossover or cross-over).tw.
46 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.
47 Placebo/
48 placebo.tw.
49 prospective.tw.
50 factorial$.tw.
51 random$.tw.
52 assign$.ab.
53 allocat$.tw.
54 volunteer$.ab.
55 or/39-54
56 38 and 55

CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature)

S36 S13 AND S35
S35 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
S34 (cheese* or dairy or egg* or fish* or gluten* or wheat* or nut* or peanut* or lactose* or yog#urt*)
S33 (MH "Nuts+")
S32 (MH "Gluten") OR (MH "Diet, Gluten-Free")
S31 (MH "Fish")
S30 (MH "Eggs")
S29 (MH "Dairy Products+")
S28 diet*
S27 (MH "Dietary Proteins+")
S26 ("amino acid*" or aminoacid* or casein* or fibre* or fiber* or prebiotic* or "pre-biotic*" or soy* or whey*)
S25 (MH "Amino Acids")
S24 (MH "Prebiotics")
S23 (hydrolys* or hydrolyz*)
S22 (formula* or bottle-fe#d* or bottlefe#d*
S21 (MH "Infant Food+")
S20 (allerg* or hypoallerg* or hypo-allerg* or hyperallerg* or hyper-allerg* or hypersensitiv* or hyper-sensitiv* or intoleran* or non-allerg* or nonallerg* or sensitiv *)
S19 (MH "Allergens")
S18 (MH "Food Hypersensitivity")
S17 (MH "Milk Hypersensitivity")
S16 (breastfe#d* OR breast-fe#d* or breastmilk or breast-milk or milk)
S15 (MH "Breast Feeding")
S14 (MH "Milk, Human")
S13 S11 OR S12
S12 (MH "Infant Colic")
S11 S7 AND S10
S10 S8 OR S9
S9 (MH "Infant+")
S8 TI(baby or babies or child* or infant* or newborn* or neonate*) OR AB(baby or babies or child* or infant* or newborn* or neonate*)
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6 (cry or crying or cries)
S5 (MH "Crying")
S4 ((gastric or gastro*) N3 (spasm* or pain* or cramp*))
S3 ((stomach or abdominal or abdomen*) N3 (spasm* or pain* or cramp*))
S2 colic*

S1 (MH "Colic")

PsycINFO Ovid

1 crying/
2 colic$.tw.
3 (cry or crying or cries).tw.
4 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw.
5 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw.
6 or/1-5
7 (baby or babies or child$ or infant$ or newborn$ or neonate$).tw.
8 (infancy 2 23 mo or neonatal birth 1 mo).ag.
9 7 or 8
10 breast feeding/
11 (breastfe?d$ or breast fe?d$ or breastmilk$ or breast-milk$ or milk$).tw.
12 bottle feeding/
13 Food Allergies/
14 antigens/
15 (allerg$ or hypoallerg$ or hypo-allerg$ or hyperallerg$ or hyper-allerg$ or hypersensitiv$ or hyper-sensitiv$ or intoleran$ or non-allerg$ or nonallerg$ or sensitiv$).tw.
16 (formula$ or bottle fed$ or bottlefed$ or bottlefeed$ or bottle feed$).tw.
17 (hydrolys$ or hydrolyz$).tw.
18 dietary supplements/
19 (amino acid$ or aminoacid$ or casein$ or fibre$ or fiber$ or prebiotic$ or pre-biotic$ or soy$ or whey$).tw.
20 Amino acids/
21 diet$.tw.
22 (cheese$ or dairy or egg$ or fish$ or gluten$ or wheat$ or nut$ or peanut$ or lactose$ or yog?urt$).tw.
23 or/10-22
24 6 and 9 and 23
25 clinical trials/
26 random$.tw.
27 (allocat$ or assign$).tw.
28 ((clinic$ or control$) adj trial$).tw.
29 ((control$ or experiment$ or intervention$) adj3 group$).tw.
30 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
31 (crossover$ or "cross over$").tw.
32 random sampling/
33 Experiment Controls/
34 Placebo/
35 placebo$.tw.
36 exp program evaluation/
37 treatment effectiveness evaluation/
38 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
39 or/25-38
40 24 and 39

Science Citation Index (SCI) and Social Sciences Citation Index (SSCI); Web of Science

12 #11 AND #10
11 TS=(random* or control* or trial* or placebo* or group* or blind* or double-blind*) .
10 #9 AND #1
9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
8 TS= (cheese* or dairy or egg* or fish* or gluten* or wheat* or nut* or peanut* or lactose* or yog*urt*)
7 TS=(hydrolys* or hydrolyz*)
6 TS=("amino acid*" or aminoacid* or casein* or fibre* or fiber* or prebiotic* or pre-biotic* or soy* or whey*)
5 TS= (allerg* or hypoallerg* or hypo-allerg* or hyperallerg* or hyper-allerg* or hypersensitiv* or hyper-sensitiv* or intoleran* or non-allerg* or nonallerg* or sensitiv *)
4 TS=(formula* or bottle-fed or bottle-feed* or bottlefeed* or bottlefed)
3 TS=(breastfed or breast-fed or breastfeed* or breast-feed*)
2 TS=(diet*)
#1 TS=((colic* or crying or cries or cry) Near/10 (infant* or baby or babies or child*))

Conference Proceedings Citation Index - Science (CPCI-S) and Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SS&H); Web of Science

#10 #9 AND #1
#9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
#8 TS= (cheese* or dairy or egg* or fish* or gluten* or wheat* or nut* or peanut* or lactose* or yog*urt*)
#7 TS=(hydrolys* or hydrolyz*)
#6 TS=("amino acid*" or aminoacid* or casein* or fibre* or fiber* or prebiotic* or pre-biotic* or soy* or whey*)
#5 TS= (allerg* or hypoallerg* or hypo-allerg* or hyperallerg* or hyper-allerg* or hypersensitiv* or hyper-sensitiv* or intoleran* or non-allerg* or nonallerg* or sensitiv *)
#4 TS=(formula* or bottle-fed or bottle-feed* or bottlefeed* or bottlefed)
#3 TS=(breastfed or breast-fed or breastfeed* or breast-feed*)
#2 TS=(diet*)
#1 TS=((colic* or crying or cries or cry) Near/10 (infant* or baby or babies or child*))

Cochrane Database of Systematic Reviews (CDSR), part of the Cochrane Library

#1[mh Colic]
#2colic*:ti,ab
#3[mh Crying]
#4(cry or crying or cries):ti,ab
#5{or #1-#4}
#6[mh Infant]
#7(baby or babies or child* or infant* or newborn* or neonate*):ti,ab
#8{or #6-#7}
#9#5 and #8
#10[mh Milk]
#11[mh "Milk, Human"]
#12[mh "Breast Feeding"]
#13(breastfeed* or "breast feed*" or breastfed or "breast fed" or breastmilk* or "breast milk*" or milk*):ti,ab
#14[mh ^Hypersensitivity]
#15[mh "Food Hypersensitivity"]
#16[mh ^Allergens]
#17[mh "Lactose Intolerance"]
#18(allerg* or hypoallerg* or hypo next allerg* or hyperallerg* or hyper next allerg* or hypersensitiv* or hyper next sensitiv* or intoleran* or non next allerg* or nonallerg* or sensitiv*):ti,ab
#19[mh "Infant Food"]
#20(formula* or bottle next fed* or bottlefed* or bottlefeed* or bottle next feed*):ti,ab
#21[mh Hydrolysis]
#22(hydrolys* or hydrolyz*):ti,ab
#23[mh Prebiotics]
#24[mh ^"Amino acids"]
#25(amino next acid* or aminoacid* or casein* or fibre* or fiber* or prebiotic* or pre next biotic* or soy* or whey*):ti,ab
#26[mh "Dietary Proteins"]
#27[mh "diet therapy"/FS]
#28diet*:ti,ab
#29[mh "Dairy Products"]
#30[mh Fishes]
#31[mh Eggs]
#32[mh Gluten]
#33[mh Nuts]
#34(cheese* or dairy or egg* or fish* or gluten* or wheat* or nut* or peanut* or lactose* or yogurt* or yoghurt*):ti,ab
#35{or #10-#34}
#36 #9 and #35 in Cochrane Reviews (Reviews and Protocols)

Database of Abstracts of Reviews of Effects (DARE), part of the Cochrane Library

#1[mh Colic]
#2colic*:ti,ab
#3[mh Crying]
#4(cry or crying or cries):ti,ab
#5{or #1-#4}
#6[mh Infant]
#7(baby or babies or child* or infant* or newborn* or neonate*):ti,ab

#8{or #6-#7}
#9#5 and #8
#10[mh Milk]
#11[mh "Milk, Human"]
#12[mh "Breast Feeding"]
#13(breastfeed* or "breast feed*" or breastfed or "breast fed" or breastmilk* or "breast milk*" or milk*):ti,ab
#14[mh ^Hypersensitivity]
#15[mh "Food Hypersensitivity"]
#16[mh ^Allergens]
#17[mh "Lactose Intolerance"]
#18(allerg* or hypoallerg* or hypo next allerg* or hyperallerg* or hyper next allerg* or hypersensitiv* or hyper next sensitiv* or intoleran* or non next allerg* or nonallerg* or sensitiv*):ti,ab
#19[mh "Infant Food"]
#20(formula* or bottle next fed* or bottlefed* or bottlefeed* or bottle next feed*):ti,ab
#21[mh Hydrolysis]
#22(hydrolys* or hydrolyz*):ti,ab
#23[mh Prebiotics]
#24[mh ^"Amino acids"]
#25(amino next acid* or aminoacid* or casein* or fibre* or fiber* or prebiotic* or pre next biotic* or soy* or whey*):ti,ab
#26[mh "Dietary Proteins"]
#27[mh "diet therapy"/FS]
#28diet*:ti,ab
#29[mh "Dairy Products"]
#30[mh Fishes]
#31[mh Eggs]
#32[mh Gluten]
#33[mh Nuts]
#34(cheese* or dairy or egg* or fish* or gluten* or wheat* or nut* or peanut* or lactose* or yogurt* or yoghurt*):ti,ab
#35{or #10-#34}
#36#9 and #35 in Other Reviews

LILACS (Latin American and Caribbean Health Science Information Database; search.bvsalud.org/portal/?lang=en)

tw:((colic* OR cries OR crying OR cry) AND (infant* OR newborn* OR neonate* OR baby OR babies OR child*)) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

IBECS (search.bvsalud.org/portal/?lang=en)

(tw:(colic* OR cries OR crying OR cry)) AND (tw:(infant* OR newborn* OR neonate* OR baby OR babies OR child*)) AND (instance:"regional") AND (db:("IBECS")) AND (instance:"regional") AND (type_of_study: ("clinical_trials"))

HomeoIndex (bases.bireme.br/cgi-bin/wxislind.exe/iah/online)

Search on : colic$ or cry$ or cries [Words] and infant$ [Words]

Networked Digital Library of Theses and Dissertations (NDLTD; www.ndltd.org)

infant* AND colic AND random*

TROVE (limited to Australian theses; trove.nla.gov.au)

Keyword: Any of the words: infant* babies
Keyword: Any of the words: colic* crying
Keyword: Any of the words: random* placebo* control* blind* group*

Limited to Books Format: Thesis

WorldCat OCLC (limited to theses; www.worldcat.org)

(ti:infant* OR babies) AND (kw:colic* OR crying) AND (kw:random* OR trial* OR control* OR blind*)

PubMed Diet Supplement subgroup (ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx)

#26 (#22 and #25) Filters: Dietary Supplements
#25 (#23 or #24) Filters: Dietary Supplements
#24 (baby [tiab] or babies [tiab] or child* [tiab] or infant [tiab] or newborn [tiab] or neonate [tiab]) Filters: Dietary Supplements
#23 infant [mh] Filters: Dietary Supplements

#22 (#9 and #21) Filters: Dietary Supplements
#21 (#18 NOT #20) Filters: Dietary Supplements
#20 ((animals [mh] NOT humans [mh])) Filters: Dietary Supplements
#18 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17) Filters: Dietary Supplements
#17 groups [tiab] Filters: Dietary Supplements
#16 trial [tiab] Filters: Dietary Supplements
#15 randomly [tiab] Filters: Dietary Supplements
#14 drug therapy [sh] Filters: Dietary Supplements
#13 placebo [tiab] Filters: Dietary Supplements
#12 randomized [tiab] Filters: Dietary Supplements
#11 controlled clinical trial [pt] Filters: Dietary Supplements
#10 randomized controlled trial [pt] Filters: Dietary Supplements
#9 (#1 or #2 or #5 or #6 or #7 or #8) Filters: Dietary Supplements
#8 (crying[tiab] or cry [tiab] or cries [tiab]) Filters: Dietary Supplements
#7 crying [mh] Filters: Dietary Supplements
#6 ((spasm* [tiab] or pain* [tiab] or cramp* [tiab])) AND (gastro* [tiab] or gastric[tiab]) Filters: Dietary Supplements
#5 (((spasm* [tiab] or pain* [tiab] or cramp* [tiab]))) AND ((stomach[tiab] or abdominal [tiab] or abdomen* [tiab]) Filters: Dietary Supplements
#2 colic* [tiab] Filters: Dietary Supplements
#1 colic [mh] Filters: Dietary Supplements

ClinicalTrials.gov (clinicaltrials.gov)

infant colic AND Study type= intervention

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; apps.who.int/trialsearch)

Basic search infant* AND crying OR infant* AND cries OR infant* AND colic*

Appendix 2. 'Risk of bias' criteria and judgements

Sequence generation for randomisation

We included only RCTs or quasi-RCTs in this review. We assessed randomisation at low risk of bias if the procedure of sequence generation was explicitly described. Examples include computer-generated random numbers, a random numbers table or coin-tossing. Where no description was given, we contacted the study authors for further information, and where we failed to receive a response, we assigned a judgment of unclear risk of bias. We considered studies to be at high risk of bias when reporting methods that were not random.

Allocation concealment

We assessed concealment of treatment allocation at low risk of bias if the procedure was explicitly described and adequate efforts were made to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment. Examples include centralised randomisation, numbered or coded containers, or sealed envelopes. We considered the following procedures to have a high risk of bias: alternation, or reference to case record numbers or dates of birth. Where no description was given, we contacted the study authors and, if we did not receive a response, we assigned a judgment of unclear risk of bias.

Blinding of parents and health professionals

In this context, the intervention is administered by parents and so, in effect, we considered them to be the target of the blinding procedures. Indeed, as the participants were less than four months of age by the defined inclusion criteria (Criteria for considering studies for this review), we deemed that this item was not applicable to them. Furthermore, parents often act as outcome assessors. We primarily assessed the risk of bias associated with the blinding of participants based on the likelihood that such blinding was sufficient to ensure that parents had no knowledge as to which intervention the infant received. We assessed blinding at low risk of bias where it was explicitly described how the parents could have no knowledge of which intervention the infant was receiving, and at high risk of bias where it was clear that parents were aware of which intervention the infant was receiving. We assessed blinding at unclear risk of bias where we did not have enough information to make an assessment of either high or low risk of bias, based on the information provided in the papers, or after contacting the study authors.

Blinding of outcome assessment

For each included study we described the methods used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we considered that the lack of blinding could not have affected the results. If blinding was not possible because of the nature of intervention, we judged the study at high risk of bias since it is possible that the lack of blinding influenced the results. We noted the blinding of health professionals where reported. Where no description was given, we contacted the study authors for more information, and where we did not receive a response, we assigned a judgment of unclear risk of bias.

Incomplete outcome data

Incomplete outcome data essentially include attrition, exclusions, and missing data.

We assigned a judgment of low risk of bias if:

1. participants included in the analysis were exactly those who were randomized into the trial, if missing outcome data were balanced in terms of numbers across intervention groups, with similar reasons for missing data across groups, or if there were no missing outcome data;
2. for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not sufficient to have a clinically relevant impact on the intervention effect estimate;
3. for continuous outcome data, the plausible effect size (SMD) among missing outcomes was not sufficient to have a clinically relevant impact on observed effect size; or
4. missing data were imputed using appropriate methods.

We assigned a judgment of high risk of bias:

1. when reasons for missing outcome data were likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups;
2. for dichotomous outcome data, when the proportion of missing outcomes compared with observed event risk was sufficient to induce clinically relevant bias in the intervention effect estimate;
3. for continuous outcome data, when the plausible effect size (SMD) among missing outcomes was sufficient to induce clinically relevant bias in the observed effect size;
4. when an 'as-treated' analysis was carried out in cases where there was substantial departure of the intervention received from that assigned at randomisation; or
5. when there was a potentially inappropriate application of simple imputation.

We assigned a judgment of unclear risk of bias:

1. when there was insufficient reporting of attrition or exclusions (or both) to permit a judgment of low or high risk of bias;
2. if the study reported incomplete outcome data; or
3. if the numbers randomized to intervention and control groups were not clearly reported.

Selective outcome reporting

We assessed the reporting of outcomes at low risk of bias if all study outcomes declared in the Methods section were reported in the Results section. We also evaluated whether different reports of the study were available, including protocols, and examined them to ensure there was no suggestion of selective outcome reporting. Where no description was given, we contacted the study authors for more information, and where no response was received, we assigned a judgment of unclear risk of bias. Where there was evidence of selective outcome reporting, we assigned a judgment of high risk of bias.

Other potential threats to validity

Where a study was at risk of other sources of bias, we assessed it at high risk of bias. For instance, sources of sponsorship or funding constitute one common example of a factor which may pose a risk of bias. We assessed each study at low risk of bias if it appeared to be free from such threats to validity. Where the risk of bias was unclear from the published information, we attempted to contact the study authors for clarification. Where this information was not forthcoming, we assessed these studies at unclear risk of bias.

WHAT'S NEW

Date	Event	Description
28 February 2019	Amended	This review has been revised to clarify reporting of data in summary versions.
1 November 2018	Amended	Typo corrected in Plain Language Summary.

CONTRIBUTIONS OF AUTHORS

Morris Gordon wrote the protocol (Savino 2014), organised retrieval of papers, wrote to study authors for additional information, supported the search, extracted and analysed data, wrote the core text of the review, and led revisions of the draft.
Elena Biagioli wrote the protocol and reviewed the Results section of the review.
Miriam Sorrenti wrote the protocol and the Discussion section of the review.
Carla Lingua added references and supported the search.
Lorenzo Moja provided statistical advice and revised key sections of the review.
Shel Banks organised retrieval of papers, wrote to study authors for additional information, supported the search, extracted and analysed data, and wrote the review.
Simone Ceratto wrote the Discussion section and contributed to the write-up of the Results section of the review.
Francesco Savino has primary responsibility for the review. He co-ordinated the efforts of the review authors. He wrote the protocol and contributed to the write-up of the Results and Discussion sections of the review.

DECLARATIONS OF INTEREST

Morris Gordon (MG) received travel grants from a number of companies during the three years leading up to publication, including from Allergan, Ferring Pharmaceuticals, Biogaia, Synergy and Tillots, to attend conferences (Advances in Inflammatory Bowel Disease, Digestive Disease Week, World Congress of Gastroentrology) and present the results of other Cochrane Reviews. These companies have had no input or involvement in any aspect of the review process during this, or previous systematic reviews carried out by MG. MG currently holds a National Institute for Health Research (NIHR) Cochrane Programme Grant, although this did not support this work. MG is a paediatrician with an interest in gastroenterology. This involves seeing patients referred with infantile colic and managing their condition in line with current, accepted, evidence-based practice. MG has no other interests to declare.

Elena Biagioli – none known.

Miriam Sorrenti – none known.

Carla Lingua – none known.

Lorenzo Moja – none known.

Shel Banks (SB) is self-employed as an Internationally Board Certified Lactation Consultant in private practice, delivering expertise in infant feeding evidence base, writing briefing papers and newsletters, etc., and delivering workshops across the northwest of England – largely for the Local Infant Feeding Information Board (LIFIB), but also the Sudden Unexpected Death of a Child (SUDC) prevention team, Lanacshire. Until March 2016, the SUDC consultant post was funded by the local authority (Lancashire County Council) via breastfeeding voluntary sector charity (Breastfeeding Network) and SB was paid by the hour. SB is also self-employed as a trainer and webinar presenter ad hoc and delivers Babyem's Open College Network Level Three and Four Maternity Nurse Training courses. Since 2009, SB has worked part-time as a Baby Friendly Co-ordinator, and she was paid for 12 months by Blackpool Teaching Hospitals NHS Foundation Trust as a Research Assistant for her work on this review. SB is Chair of LIFIB, Chair of the Communications Team, Chair of the Breastfeeding Festival, Committee Member of the Lactation Consultants of Great Britain, and a Trustee of the UK Association of Milk Banking, all of which are voluntary positions, although SB's travel expenses to meetings are paid. SB received travel expenses from Manchester City Council for speaking at their event 'Make Manchester a Breastfeeding Friendly City' in June 2018. SB has sat as a lay member on the Guideline Development Committee of three NICE Guidelines (Milk Banking, Postnatal Care Quality Standards and Faltering Growth), and was paid an honorarium by NICE (National Institute for Health and Care Excellence) for her services. SB declares that neither she personally, nor any of the entities she represents, take funding of any kind from any commercial interests in infant feeding or early years, and that she works completely within the professional code of ethics as an Internationally Board Certified Lactation Consultant. SB has no other interests to declare.

Simone Ceratto (SC) received travel grants from Nóos S.r.l and Nestlé, to attend scientific meetings. SC declares that he attended 'Campus Angelini 2017', which was sponsored by Angelini.

Francesco Savino (FS) received payment from: Danone Nutricia Middle-East DMCC, Dubai, United Arab Emirates, and Innova Pharma SpA Recordati SpA, Milan, Italy, for talks at symposiums; Società Italiana di Pediatria, Milan, Italy, for speaking at the XX Congresso Nazionale SIAIP, sponsored by Biomedia srl, Milan; HiPP GmbH & Co, Vertrieb KG, Pfaffenhofen, Germany, for consultancy work; and from Aretrè srl, Milan, Italy, for development of educational materials, outside the submitted work. FS also received a travel grant from Noos Roma, Italy, to attend ESPGHAN's 51st Annual Meeting, Geneva, and receives royalties from Springer Verlag, Milan, Italy, for the book *Nutrizione Parenterale in Pediatria.* FS declares that these organizations have had no input or involvement in any aspect of the review process during this, or previous systematic review that he has carried out. FS has no other interests to declare.

Disclaimer: the views contained herein are those of the authors and not necessarily those of the Department of Health, NHS NICE or NIHR.

SOURCES OF SUPPORT

Internal sources

- Department of Pediatrics, Regina Margherita Children's Hospital, Città della Salute e della Scienza, Turin, Italy.

  Logistical support

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Please see our protocol (Savino 2014).

Authors

Valentina Tarasco left the review team and was replaced by Shel Banks and Simone Ceratto.

Morris Gordon took over as lead author.

Types of outcome measures

We reworded the outcomes of 'reduction in the duration of crying' and 'reduction in frequency of crying episodes per 24 h, to the following more neutral formulations, to reflect the fact that we are assessing the variable rather than a reduction in the variable: 'duration of crying' and 'frequency of crying episodes per 24 h'.

We planned on defining responders as a 50% reduction in crying. However, the peer reviewers raised questions as to the external basis for this decision, so we decided to revert to a more standard definition of 'responders', as defined by primary studies. As no study reported outcomes in this area with utility for analysis, this did not impact the analysis or findings.

Originally, we planned on reporting only change scores for the primary outcome; however, many studies reported only postintervention data, and so we decided to include these too.

We planned further analyses according to each specific adverse effect when the primary studies provided sufficient data. However, we did not complete this analysis as such data were not presented, with adverse effects rarely encountered.

In addition, we included the outcome 'parental satisfaction' in Summary of findings for the main comparison, but this was not in our protocol (Savino 2014). We modified the Methods sections accordingly.

See Types of outcome measures.

Search methods for identification of studies

In order to ensure our search was as up-to-date as possible, we searched two additional databases, which are updated daily (Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE Epub Ahead of Print). See Electronic searches.

Selection of studies

We clarified that we excluded stand-alone abstracts from this review. Given the extreme complexity of the studies found, including issues of heterogeneity of specific interventions, patient characteristics and outcomes reported, as well as the poor quality of the abstracts found within the search, the team decided not to consider abstracts unless they related to a study for which we also had a full-text report. See Selection of studies.

Measures of treatment effect:

Dichotomous data

We planned to present dichotomous outcome data as risk ratios (RR), since the effects of the RR are readily understood (Walter 2000). We report all outcome data with their associated 95% CIs and P values (where possible). Using control event risks from the included trials, we planned to calculate the number needed to treat to benefit (NNTB) and its associated 95% CI for statistically significant dichotomous outcomes.

Continuous data

If all studies used the same measurement scale, we intended to calculate the mean difference (MD) for change scores. Where studies used different scales, we planned to calculate the standardised mean difference (SMD) using Hedges' g. Where necessary, we calculated effect

estimates from P values, *t* statistics, analysis of variance (ANOVA) tables or other statistics, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

To analyse continuous data, we planned to use, according to need, either change scores or final values without combining them. However, no such analysis was possible due to a lack of data.

Had both continuous and dichotomous data been available for an outcome, we planned to include only the continuous outcome in the primary analysis. We planned that when studies had reported an outcome as a dichotomous measure, and others had used a continuous measure of the same construct, to convert the results for the former from the dichotomous measure to a standardised mean difference, provided that we could assume the underlying continuous measure had an approximately normal or logistic distribution (otherwise we would have carried out two separate analyses). However, no such analysis was possible due to a lack of data. See Measures of treatment effect.

Unit of analysis issues

Studies with multiple treatment arms

Had our strategy to combine data to make single, pair-wise comparisons prevented investigation of potential sources of heterogeneity, we planned to analyse each formula separately (against a common control group – placebo), but divide the sample size for common comparator arms proportionately across each comparison (Higgins 2011b). This simple approach allows the use of standard software (including RevMan 2014), and prevents the inappropriate double-counting of individuals; however, it was not needed due to a lack of data. Additionally, concerns with the length of a reasonable washout period existed and further limited scope for such analysis.

Cross-over studies

For cross-over trials, we planned to used the mean and standard error of the paired analysis for the meta-analysis; however, this was not possible due to a lack of data. In future updates of this review, should we have sufficient data, we will include both parallel and cross-over studies with an adequate washout period in a meta-analysis using the inverse variance method, as recommended by Elbourne 2002; in the meta-analysis, the weight of each study is inversely proportional to the variance (one over the square of the standard error) (Deeks 2017). We will include cross-over studies with an inadequate washout period in a meta-analysis using the data from the first arm only. Even though this method excludes some of the data, it avoids the inappropriate consideration of correlated information.

See Unit of analysis issues.

Dealing with missing data

For all outcomes in all studies, we planned to carry out analyses as far as possible on an intention-to-treat basis; that is, we planned to attempt to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated regardless of whether or not they received the allocated intervention. For missing continuous data, we intended to estimate standard deviations from other available data, such as standard errors, or impute them using the methods suggested in Higgins 2011b. For loss to follow-up for continuous data, we planned to base analyses on those participants completing the trial, essentially assuming that outcome was the same in the missing participants and the observed participants. Where there was a discrepancy between the number randomised and the number analysed in each treatment group, we intended to calculate and reported the percentage lost to follow-up in each group. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by conducting sensitivity analyses (see Sensitivity analysis).

Data synthesis

Where interventions were similar in terms of type of dietary modification, type of outcome assessed and type of colic, we planned to group studies and synthesised their results in a meta-analysis. Because we assumed that clinical heterogeneity was very likely to impact on our results, given the wide breadth and types of interventions included, we intended to combine studies using a random-effects model, irrespective of statistical evidence of heterogeneity. We planned to calculate all overall effects using inverse variance methods and carried out statistical analysis using RevMan 5 (RevMan 2014).We included a new section on 'Assessment of the quality of the evidence' at the request of the editorial base. See Data synthesis.

Assessment of heterogeneity

We planned to assess statistical heterogeneity by examining the I^2 statistic (Deeks 2017), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error. We interpreted the I^2 statistic as suggested in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

1. 0% to 40%: might not be important.
2. 30% to 60%: may represent moderate heterogeneity.
3. 50% to 90%: may represent substantial heterogeneity.
4. 75% to 100%: considerable heterogeneity.

We also evaluated the CI for the I^2 statistic. In addition, we employed a Chi^2 test of homogeneity, with a 10% level of significance, to determine the strength of the evidence that the heterogeneity was genuine.

Subgroup analysis and investigation of heterogeneity

Large numbers of subgroup analyses may lead to misleading conclusions (Oxman 1992; Yusuf 1991). We planned to conduct the following subgroup analyses,

1. Age of mother at time of birth (21 years and younger versus older than 21 years).
2. Type of feeding (formula-fed versus breastfed).
3. Atopy (lower versus higher risk of atopy).
4. Follow-up (less than four weeks of treatment versus more than four weeks of treatment).
5. Trial quality (low quality (lack of allocation concealment or lack of blinding) versus high quality (allocation concealment and blinding)).

Sensitivity analysis

We planned to conduct sensitivity analyses to determine whether findings were sensitive to restricting the analyses to studies judged to be at low risk of bias for blinded assessment of the primary outcome. In addition, we planned to assess the sensitivity of findings to any imputed data, by calculating the treatment effect including and excluding the imputed data, to see whether this altered the outcome of the analysis. We planned to investigate the effect of dropouts and exclusions by conducting worst- versus best-case scenario analyses. We analysed the effect of using the stringent Wessel 1954 definition of infant colic, the more recent definition given by Drossman 2016 and other variants.

Additional references

We updated our references to the latest versions of Chapters 8, Higgins 2017, and 9, Deeks 2017, in the*Cochrane Handbook for Systematic Reviews of Interventions*.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula; Allergens; Colic [*diet therapy]; Crying; Diet Therapy [methods]; Lactase [administration & dosage]; Randomized Controlled Trials as Topic; Soybean Proteins [administration & dosage]; Time Factors

MeSH check words

Female; Humans; Infant; Male