Dietary modifications for infantile colic (Protocol)

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[Intervention Protocol]

Dietary modifications for infantile colic

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

BACKGROUND

Description of the condition

Infantile colic can be defined as periods of inconsolable, unexplained, and incessant crying in a seemingly healthy infant that, quite understandably, leads to exhausted, frustrated, and concerned parents seeking to comfort their child (Landgren 2010). The prevalence of excessive crying varies according to the definition used although, most often, it peaks during the second month of life, with a prevalence of 1.5% to 11.9% (Reijneveld 2001). Traditionally, the definition of the condition was based on the rule of three (Wessel 1954): that is, unexplained episodes of paroxysmal crying for more than three hours per day, for three days per week, for at least three weeks. More recently a new definition has been proposed. It refers to a clinical condition of fussing and crying for at least one week in an otherwise healthy infant (Hyman 2006). Colic can be graded as mild, moderate, or severe, though there is no consensus for this classification. Colic can affect up to 10% to 30% of infants worldwide (Clifford 2002; Rosen 2007).

Paroxysms of inconsolable crying 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 (Savino 2010). Symptoms typically start in the second week of life, in both breast-fed and formula-fed infants, and usually resolve by three months of age (Lucas 1998). Generally speaking, these symptoms are not indicative of disease and thus hospital admission for these infants is generally unnecessary, detrimental, and should not be encouraged (Savino 2007). However, about 5% of colicky crying infants do have a serious, underlying medical problem (Freedman 2009; Savino 2005; Savino 2007). Therefore, all colicky infants should undergo a complete medical assessment in order to exclude underlying medical conditions that require investigation and treatment (Savino 2010).

The etiopathogenesis 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. It has been suggested that a number of behavioral factors (psychological and social) and biological components (food hypersensitivity, allergy, or both, gut microflora, and dysmotility) can con-

tribute to its manifestation (Gupta 2007). These include the following.

First, lactose intolerance - due to a relative lactase deficiency - has been identified as a possible causative factor in infant colic. Carbohydrate malabsorption leads to the colonic fermentation of sugars and an increase in the 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, increases in breath hydrogen levels have been reported (Moore 1988; Hyams 1989; Miller 1990).

Second, the immunological model of colic focuses on possible allergens, such as cow's milk proteins in breast milk or infant formula, as the cause of colic. Intact proteins from the mother's diet cross over into the breast milk and provoke an allergic response and symptoms of colic in some infants. Consequently, a low-allergen maternal diet has been proposed as a form of treatment (Hill 2005; Schach 2002). The possibility that infantile colic could be related to allergens was first described by Shannon 1921. Since then, a number of studies have evaluated the possible association between colic and food hypersensitivity (Lothe 1982; Jakobsson 1983; Campbell 1989; Forsyth 1989; Lothe 1989; Iacono 1991; Hill 1995; Lindberg 1999; Estep 2000; Lucassen 2000; Hill 2005). The evidence shows that about 25% of infants with moderate or severe symptoms have cow's milk protein-dependent colic (Axelsson 1986; Lindberg 1999; Hill 2000) that improves after some days of a hypoallergenic diet (Jakobsson 1983, Jakobsson 2000, Campbell 1989, Lothe 1989, Estep 2000, Savino 2001, Iacono 1991, Iacono 2005, Dupont 2010). For these infants, infantile colic could be the first manifestation of atopic disease and, for this reason dietetic treatment should be the first therapeutic approach (Gupta 2007, Savino 2010, Perry 2011, Hall 2012). Indeed, dietary changes, such as eliminating cow's milk proteins, are particularly indicated in cases of suspected intolerance to cow milk proteins (for example, in infants with a positive family history, eczema or onset after the first month of life, and colic associated with other GI symptoms such as vomiting or diarrhea) (Jakobsson 1983; Hill 1995; Lucassen 2000; Hill 2005).

Third, there is growing evidence that the intestinal microbiota in colicky infants differ from those in healthy controls, since higher levels of anaerobic bacteria, such as coliform and *Escherichia coli*, and a lower concentration of lactobacilli have been reported in infants with colic (Savino 2010). Human milk naturally contains these prebiotics; they are defined as indigestible oligosaccharides that could selectively enhance the proliferation of certain probiotic bacteria in the colon, especially Bifidobacterium species (Thomas 2010). However, studies have failed to find a protective effect of breast feeding on the development of colic in breast-fed infants (Clifford 2002), while recent evidence suggests that oligosaccharide prebiotics (a mixture of oligosaccharides 0.8 g/100 mL, comprising 90% galacto-oligosaccharides and 10% fructo-oligosaccharides (Savino 2006)), may be effective treatments for crying in formula-fed infants with colic.

Description of the intervention

Dietary modifications have often been suggested both for breast-fed and formula-fed infants. We will examine the following dietary interventions for infantile colic:

Dietary modifications for breast-fed, colicky infants who are allergic to certain foods (milk, yogurt, cheese) 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 breast-feeding mothers consumed a hypoallergenic diet (Jakobsson 1983, Axelsson 1986, Lothe 1989, Lothe 1990, Clyne 1991). For example, Hill 2005 demonstrated that a monitored low-allergen maternal diet, which excludes cow's milk, eggs, peanuts, tree nuts, wheat, soy, and fish, leads to a reduction in distressed behavior. A brief interruption of breastfeeding and a temporary substitution with an amino-acid-based formula has also been proposed (Estep 2000); however, this intervention could have negative effects on maternal-infant interaction and should be considered as a last resort for severely and selected colicky infants (Savino 2001, Savino 2007, Savino 2010).

For formula-fed colicky infants, dietary modifications involve decreasing or removing the intake of cow's 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 hydrolyzed formula, casein hydrolyzed formula, amino-acid based formula, partially hydrolyzed formula, low-lactose milk formula, formula with prebiotic, etc). Some trials have been performed using formulas containing partially hydrolyzed whey proteins, low amounts of lactose, prebiotic oligosaccharides, and a high beta palmitic acid content (Oggero 1994, Savino 2005, Savino 2006, Osborn 2013). In bottle-fed babies, where an underlying allergy to cow's milk protein is hypothesized to affect the infant, extensively hydrolyzed formulas, based on casein or whey, have been shown to reduce colic symptoms (Forsyth 1989, Lothe 1989, Jakobsson 2000, Lucassen 2000, Gupta 2007, Cohen-Silver 2009). Other studies, hypothesizing 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 (Moore 1988; Hyams 1989Savino 2003; Infante 2011).

It has also been suggested that soy formulas may reduce symptoms of colic in some bottle-fed infants. However, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition reasoned recently that there is no evidence to support the use of soy formulas in the management of colic. Additionally, due to concerns regarding a crossover allergy to cow's milk protein and their estrogen content, it is advised that such formulas should not be given to infants with a food allergy during the first six months of life (Agostoni 2006).

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

Dietary interventions have been investigated as a means to reduce colic in many published studies (Campbell 1989; Clifford 2002; Clyne 1991); they have proposed a link between infant crying and the gastrointestinal (GI) tract, thereby implicating the role of nutritional factors such as lactose, lipids and cow milk proteins (Jakobsson 1983; Jakobsson 2000; Lindberg 1999; Feinle-Bisset 2013).

Several pathophysiological mechanisms have been proposed as a rational basis for the therapeutic use of dietary interventions, including immuno-modulatory and anti-inflammatory actions, and effects on motility and pain perception (Hill 2000 ; Hyman 2006; Gupta 2007).

There is growing evidence that colicky infants show gut dysfunctions, involving hypersensitivity and abnormal motility, so that physiological stimuli, that in normal subjects are unperceived, are able to induce pain symptoms, fussing and increased crying (Heine 2008; Savino 2007). However the exact mechanisms by which cow's milk and other food allergens induce GI motility disorders need further investigation (Heine 2006; Farré 2013).

Why it is important to do this review

A number of studies and reviews of the evidence (Garrison 2000; Lucassen 2001; Cohen-Silver 2009; Savino 2010; Perry 2011; Hall 2012) suggest that dietary interventions may be effective in reducing the symptoms of both breast-fed and formula-fed infants with colic. Potential interventions have included a low-allergen diet for mothers of breast-fed infants (Hill 2005), and hydrolyzed formulas (Forsyth 1989; Jakobsson 2000; Lucassen 2000), or low-lactose content formulas for formula-fed infants (Savino 2003; Savino 2006; Infante 2011). This systematic review examines the effectiveness and safety of dietary modifications for infantile colic, distinguishing between breast-fed and formula-fed infants. Although a recent systematic review on this topic has been published (Iacovou 2012), the search was performed in 2010, and excluded all unpublished and grey literature. An up-to-date systematic review using the Cochrane methodology is required.

OBJECTIVES

To assess the effectiveness and safety 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

Randomized and quasi-randomized controlled trials.

Types of participants

Infants younger than four months suffering from infantile colic (whether breast-fed or formula-fed), as defined by the study. Both breast-fed and formula-fed infants will be eligible.

Types of interventions

The purpose of this review is to compare any one of the following dietary interventions, alone or in combination, versus another intervention(s) or placebo.

Breast-fed infants

- 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
- Low-allergen breast-feeding diet
- A diet plan or dietary supplementation, regardless of duration of intervention

Formula-fed infants

- Soy-based formula
- Extensively hydrolyzed formula based on whey or casein
- Partially hydrolyzed formula
- Formula with low or no content of lactose
- Amino-acid based formula
- Formula that includes prebiotics

We will exclude studies involving probiotics. For further information on these interventions, we direct authors to the following Cochrane Review: 'Oral probiotics for infantile colic' (Praveen 2014).

Types of outcome measures

Primary outcomes

1. A reduction in the duration of crying (post-treatment versus baseline)*. Data may be continuous (for example, hours per day), or dichotomous (for example, reduction under a predefined threshold, as determined by the trial authors)

Secondary outcomes

1. The number of responders in each group after treatment*. Responders will be defined as those who experienced a decrease in the daily, average crying time of 50% from baseline* (dichotomous outcome)
2. Reduction in frequency of crying episodes per 24 hours (post-treatment versus baseline)* (dichotomous outcome)
3. Parental or family quality of life, including measures of parental stress, anxiety or depression* (continuous outcome)
4. Infant sleep duration per 24 hours at 7, 14, and 21 days* (post-treatment 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*, diarrhea, apnea, apparent life-threatening events, and lethargy (dichotomous outcome)

We will analyze the frequency of all adverse events in each study group. We will conduct further analyses according to each specific adverse event if sufficient data are provided by the primary studies.
Timing of outcome assessment: we will include outcomes evaluated after the completion of any treatment protocol (that is any period, any number of treatments), and also at later follow up, if reported. Outcomes indicated by an asterisk (*) will be used to populate the 'Summary of findings' table for the main comparison, where data permit. Where data are insufficient, we will provide a narrative account of the outcomes.

Search methods for identification of studies

We will identify relevant trials by searching the following electronic sources:

1. Cochrane Central Register of Controlled Trials (CENTRAL), part of The Cochrane Library;
2. Ovid MEDLINE;
3. Embase;
4. CINAHL;
5. PsycINFO;
6. Science Citation Index;
7. Social Sciences Citation Index;
8. LILACS;
9. IBECS;
10. HOMEOINDEX;
11. PubMed Dietary Supplement Subset (PubMed_Dietary_Supplement_Subset.aspx)
12. Cochrane Database of Systematic Reviews, part of The Cochrane Library;
13. Database of Abstracts of Reviews of Effects (DARE);
14. Conference Proceedings Citation Index - Science;
15. Conference Proceedings Citation Index - Social Science & Humanities;
16. International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
17. ClinicalTrials.gov (clinicaltrials.gov/);
18. WorldCat (limited to theses) (worldcat.org/);
19. Networked Digital Library of Theses and Dissertations (ndltd.org/);
20. TROVE (limited to Australian theses) (trove.nla.gov.au/);

We will not impose any date or language restrictions. Studies published in a non-English language will be professionally translated in full. We will collate references in EndNote and remove any duplicates.
There is some evidence that data from abstracts can be inconsistent with data in published articles (Pitkin 1999). Therefore, abstract publications will not be included in this review.

Electronic searches

We will adapt the following Ovid MEDLINE search strategy for each database. The study methods filter is the Cochrane highly sensitive search strategy for identifying randomized or quasi-randomized trials (sensitivity maximizing version), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2008).

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$).tw.
10 8 or 9
11 7 and 10
12 milk/
13 milk, human/
14 (breastfe?d$ or breastmilk$ or breast-milk$ or milk$).tw.
15 Hypersensitivity/
16 exp Food Hypersensitivity/
17 Allergens/
18 Lactose Intolerance/
19 (allerg$ or hyperallerg$ or hyper-allerg$ or hypersensitiv$ or hyper-sensitiv$ or intoleran$ or non-allerg$ or nonallerg$ or sensitiv$).tw.
20 exp infant food/
21 (formula$ or bottle fed$ or bottlefed$ or bottlefeed$ or bottle feed$).tw.
22 Hydrolysis/
23 (hydrolys$ or hydrolyz$).tw.
24 prebiotics/
25 Amino acids/

26 (amino acid$ or aminoacid$ or casein$ or fibre$ or fiber$ or prebiotic$ or pre-biotic$ or soy$ or whey$).tw.
27 exp Dietary Proteins/
28 diet therapy.fs.
29 diet$.tw.
30 exp Dairy Products/
31 exp Eggs/
32 fishes/
33 gluten/
34 Nuts/
35 (cheese$ or dairy or egg$ or fish$ or gluten$ or wheat$ or nut$ or peanut$ or lactose$ or yog?urt$).tw.
36 or/12-35
37 11 and 36
38 randomized controlled trial.pt.
39 controlled clinical trial.pt.
40 randomi#ed.ab.
41 placebo$.ab.
42 drug therapy.fs.
43 randomly.ab.
44 trial.ab.
45 groups.ab.
46 or/38-45
47 exp animals/ not humans.sh.
48 46 not 47
49 37 and 48

Searching other resources

We will search the bibliographies of included studies to identify any other potentially relevant articles.

Grey literature

We will search Google and Google Scholar using the main search terms. We will handsearch conference proceedings from the ESPGHAN annual scientific meeting from the past two years to identify other potentially relevant studies that may not be published in full. Where references to relevant unpublished or ongoing studies are identified, we will record them, and make attempts to obtain sufficient information to incorporate them in this review. Studies from the grey literature will only be included if sufficient data are presented. If data are not complete, we will contact the authors in order to verify the eligibility of the study.

Data collection and analysis

Selection of studies

Two reviewers (FS; MS) will independently screen titles, abstracts, and full reports for eligibility against the inclusion criteria (see above).

Specifically, we will:
1. merge search results using reference management software and remove duplicate records of the same report;
2. examine titles and abstracts to remove irrelevant reports;
3. retrieve full texts of potentially relevant reports;
4. link together multiple reports of the same study;
5. examine full text reports for studies which meet the eligibility criteria;
6. correspond with investigators, when appropriate, to clarify study eligibility;
7. at all stages, note reasons for inclusion and exclusion of articles, resolving any disagreements through consensus;
8. make final decisions on study inclusions and resolve any discrepancies through a process of consensus;
9. proceed to data collection.

Data extraction and management

We will develop data extraction forms *a priori*, as per the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008a). We will extract the following information.

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 (breast feeding, bottle feeding), age at onset of colic, age at commencement of intervention, and evaluation of potential effect modifiers (for example, age, gender).
2. Interventions and controls: number of groups, intervention(s) applied, frequency and duration of treatment, total number of treatments, permitted cointerventions.
3. Methods: study design, duration, sequence generation, allocation concealment, blinding of outcome assessors, evaluation of success of blinding.
4. Outcomes: list of outcomes assessed, definitions used, values of means and standard deviations at baseline and at time points, as defined by the study protocol (or change from baseline measures, if given).
5. Results: measures at end of protocol, 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 authors, comments from the authors, key conclusions from the study (by the authors), other comments from review authors.

Two review authors (FS; MS) will extract the data independently using the data extraction form. A third review author (VT) will resolve any disagreements. We will collate data in the latest version of Review Manager (RevMan) (Review Manager 2011).

Assessment of risk of bias in included studies

Two review authors (FS; MS) will independently evaluate each study for risk of bias using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008b, Deeks 2011) for the following domains: sequence generation; allocation concealment; blinding of parents, health professionals, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. We will judge each domain as being at 'low', 'high', or 'unclear' risk of bias. We will compare the judgments, and discuss and resolve any inconsistencies in the assessments. A third review (VT) author will resolve any persisting disagreements.

Sequence generation for randomisation

We will include only randomized controlled trials or quasi-randomized controlled trials in the study. We will assess randomization as being 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. If no description is given, we will contact the authors for further information, and if we fail to receive a response, we will assign a judgment of unclear risk of bias. We will consider studies that use non-randomized procedures to have a high risk of bias.

Allocation concealment

We will assess concealment of treatment allocation as being 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, enrollment. Examples include centralized randomization, numbered or coded containers, or sealed envelopes. Procedures considered to have a high risk of bias include alternation, or reference to case record numbers or dates of birth. If no description is given, we will contact the study authors and, if no response is received, we will assign a judgment of unclear risk of bias. If allocation concealment did not occur, we will assign a judgment of high risk of bias.

Blinding of parents, health professionals, and outcome assessors

In this context, the intervention is administered by parents and so, in effect, they will be considered the target of the blinding procedures. Indeed, as the participants will be less than four months of age, by the defined inclusion criteria, it is deemed that this item is not applicable to them. Furthermore, parents often act as outcome assessors. We will primarily assess 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 will describe, for each included study, the methods used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. We will judge studies to be at low risk of bias if they were blinded, or if we consider that the lack of blinding could not have affected the results. If blinding was not possible because of the nature of intervention, we will judge the study to be at high risk of bias because it is possible that the lack of blinding influenced the results. We will note the blinding of health professionals if reported.

If no description is given, we will contact the study authors for more information, and if we do not receive a response, we will assign a judgment of unclear risk of bias. If not blinded, we will assign a judgment of high risk of bias.

Incomplete outcome data

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

We will assign a judgment of low risk of bias:

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

We will assign a judgment of high risk of bias for any one of the following reasons:

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

We will assign a judgment of unclear risk of bias:

- when there is insufficient reporting of attrition and/or exclusions to permit a judgment of a low or high risk of bias;
- if the study reported incomplete outcome data;
- if the numbers randomized to intervention and control groups are not clearly reported.

Selective outcome reporting

We will assess the reporting of outcomes as being at low risk of bias if all the study outcomes declared in the methods section have been reported in the results. We will also evaluate whether different reports of the study are available, including protocols, and examine them to ensure there is no suggestion of selective outcome reporting. If no description is given, we will contact the authors for more information, and if no response is received, we will assign a judgment of unclear risk of bias. If there is evidence of selective reporting, we will assign a judgment of high risk of bias.

Other potential threats to validity

If the study is at risk of other sources of bias, we will assess it as being at high risk of bias. For instance, if it was stopped early due to a data-dependent process or having a baseline imbalance between the groups. Examples of factors that may pose a risk of bias could include sources of sponsorship or funding. We will assess the study as being at low risk of bias if it appears to be free from such threats to validity. Where the risk of bias is unclear from published information, we will attempt to contact authors for clarification. If this is not forthcoming, we will assess these studies as being at unclear risk of bias.

Assessment of overall risk of bias

We will assess the overall quality of evidence using the GRADE approach (Guyatt 2008). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect, or association, reflects the item being assessed. Randomized trials 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 will determine the overall quality of the evidence for each outcome after considering each of these factors, and will grade them as follows:

- high: further research is very unlikely to change confidence in the estimate of effect;
- moderate: further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate;
- low: further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate;
- very low: any estimate of effect is very uncertain.

Measures of treatment effect

Dichotomous data

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

Continuous data

If all studies use the same measurement scale, we will calculate mean differences (MD) for change scores. Where studies use different scales, we will calculate the standardized mean differences (SMD) using *Hedges g*. If necessary, we will calculate effect estimates from P values, *t* statistics, analysis of variance (ANOVA) tables, or other statistics as recommended in the *Cochrane Handbook for Systematic Review of Interventions* (Deeks 2011).
For this analysis we will use, according to need, either change scores or final values without combining them.
If both continuous and dichotomous data are available for an outcome, we will include only the continuous outcome in the primary analysis. If some studies report an outcome as a dichotomous measure, and others use a continuous measure of the same construct, we will convert the results for the former from the dichotomous measure to a SMD, provided that we can assume the underlying continuous measure has approximately a normal or logistic distribution (otherwise we will carry out two separate analyses).

Unit of analysis issues

For each included study, we will determine whether the unit of analysis is appropriate for the unit of randomization and the design of that study (that is, whether the number of observations matches the number of 'units' that were randomized (Deeks 2008)). It is unlikely that we will find cluster-randomized trials because this design is uncommon in this field. However, if we do, we will use the intraclass correlation coefficient (ICC) to convert trials to their effective sample size before incorporating them into the meta-analysis, as recommended in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2008c). Where the ICC is not provided we will use values available in the published literature (Campbell 2000).

Studies with multiple treatment arms

In the primary analysis, we will combine results across all eligible intervention (dietary change, i.e. special formula) arms, and

compare them with the combined results across all eligible control arms (another intervention(s) or placebo), making single, pairwise comparisons. Where such a strategy prevents investigation of potential sources of heterogeneity, we will analyze each formula separately (against a common control group - placebo), but divide the sample size for common comparator arms proportionately across each comparison (Higgins 2008c). This simple approach allows the use of standard software (including RevMan) (Review Manager 2011), and prevents the inappropriate double-counting of individuals.

Cross-over studies

In randomized cross-over studies, individuals receive each intervention sequentially, in a random order. Cross-over studies usually contain a washout period, which is a stage after the first treatment but before the second treatment, where time is given for the active effects of the first treatment to wear off before the new treatment begins (that is, to reduce the carry-over effect). A concern with the cross-over design is the risk of a carry-over effect when the first treatment affects the second. Inadequate washouts are seen when the carry-over effects persist after the washout period. For this review, we considered an adequate washout period for cross-over studies to be a minimum of one day because the food transit time of milk cannot last more than 24 hours.

When including both parallel and cross-over studies with an adequate washout period, we will use 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 2008). When including cross-over studies with an inadequate washout period, we will use only the data from the first arm. Even though this method excludes some of the data, it avoids the inappropriate consideration of correlated information. If cross-over trials are reported, we will use the mean and standard error of the paired analysis for the meta-analysis.

Dealing with missing data

Where data are missing, we will contact the corresponding authors of included studies to supply any unreported data. For all outcomes, in all studies, we will carry out analyses as far as possible on an intention-to-treat basis; that is, we will attempt to include all participants randomized to each group in the analyses, and we will analyze all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. For continuous data that are missing, we will estimate standard deviations from other available data, such as standard errors, or we will impute them using the methods suggested in Higgins 2008c. We will make no assumptions about loss to follow up for continuous data, and we will base analyses on those participants completing the trial. If there is a discrepancy between the number randomized and the number analyzed in each treatment group, we will calculate and report the percentage lost to follow up in each group. Where it is not possible to obtain missing data, we will record this in the data collection form, report it in the 'Risk of bias' table, and discuss the extent to which the missing data could alter the results and, hence, the conclusions of the review. For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by conducting sensitivity analyses.

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing the distribution of important participant characteristics between trials (for example, age) and trial characteristics (randomization, concealment, blinding of outcome assessment, losses to follow up, treatment type, cointerventions). We will assess statistical heterogeneity by examining the I^2 statistic (Deeks 2008), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error.

We will interpret the I^2 statistic as suggested in the latest version of Deeks 2011:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: suggests considerable heterogeneity.

We will also evaluate the confidence interval for the I^2 statistic.

In addition, we will employ a Chi^2 test of homogeneity, with a 10% level of significance, to determine the strength of evidence that heterogeneity is genuine.

Assessment of reporting biases

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

In addition, if there are more than 10 studies grouped in a comparison, we will evaluate whether reporting biases are present by using funnel plots to investigate any relationship between effect estimates and study size and/or precision, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2008).

Data synthesis

Where interventions are similar in i) type of dietary modification, ii) type of outcome assessed, and iii) type of colic, we plan to group the studies and synthesize their results in a meta-analysis. We will present results for each combination of dietary regimen, assessed outcome, and colic type, with the exception of those studies for which no data are observed. For instance, if two or more studies

assessed the effects of hypoallergenic formula in otherwise healthy children with colic and both measured the daily crying, we will perform a meta-analysis of the results. Because we assume that clinical heterogeneity is very likely to impact on our review results, given the wide breadth and types of interventions included, we will combine the studies using a random-effects model, regardless of statistical evidence of heterogeneity effect sizes. We will calculate all overall effects using inverse variance methods.

We will carry out statistical analysis using RevMan (Review Manager 2011).

Subgroup analysis and investigation of heterogeneity

Large numbers of subgroup analyses may lead to misleading conclusions (Yusuf 1991; Oxman 1992). These analyses will be exploratory as they involve non-experimental (cross-study) comparisons and will involve primary outcomes. We will treat any conclusions with caution. We plan to carry out the following subgroup analyses:

- age of mother at time of birth (younger versus older; that is, 21 years and younger versus older than 21 years);
- type of feeding (bottle fed versus breast fed);
- atopy (lower versus higher risk of atopy);
- short-term and long-term follow up (fewer versus more than four weeks of treatment);
- low-quality trials versus high-quality trials (allocation concealment versus lack of allocation concealment; blinding versus lack of blinding).

Sensitivity analysis

We will conduct sensitivity analyses to determine whether findings are 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 will assess the sensitivity of findings to any imputed data, by calculating the treatment effect including and excluding the imputed data to see whether this alters the outcome of the analysis. We will investigate the effect of drop-outs and exclusions by conducting worst- versus best-case scenario analyses. We will also analyze the effect of using the stringent Wessel definition of infant colic (Wessel 1954), the more recent definition given by Hyman 2006, or a non-recognized definition.

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

Francesco Savino - co-ordinated the efforts of the authors, organized retrieval of papers, wrote to authors for additional information.

Valentina Tarasco - wrote the protocol and will carry out the search.

Miriam Sorrenti - wrote the protocol and will carry out the search.

Carla Lingua - will add the references and support the search.

Lorenzo Moja - provided statistical advice.

Morris Gordon - wrote the protocol.

Elena Biagioli - will perform the statistical analyses.

DECLARATIONS OF INTEREST

Francesco Savino - reports a travel grant from Nestlé Italy; personal fees from Mead Johnson Nutrition Italy; personal fees from Cana S.A.S., Thessaloniki, Greece; personal fees from Nutricia - Part of Group Danone, Dubai, Kuwait; travel grants and others from BioGaia AB, Stockholm, Sweden; personal fees from HiPP GmbH & Co Vertrieb KG, Germany; travel grant from Nestlé France S.A.S., Paris; travel grants and others from Noos, Srl, Roma, Italy; personal fees from A. Menarini IFR Srl, Firenze, Italy, outside the submitted work. These organizations have had no input or involvement in any aspect of the review process during this, or previous, systematic reviews carried out by Francesco Savino. There are no other interests to declare.

Valentina Tarasco - none known.

Miriam Sorrenti - none known.

Carla Lingua - none known.

Lorenzo Moja - none known.

Morris Gordon - has received a travel grant from companies, including Abbott, Warner Chilcott, Norgine Pharmaceuticals, Ferring Pharmaceuticals, and Cassen Fleet, to attend conferences to present the results of a previous review. These companies have had no input or involvement in any aspect of the review process during this, or previous, systematic reviews carried out by Morris Gordon. Also, he has received an honorarium from Danone for clinical editorial duties on an atlas of infant nutrition produced by Mardeno Atlases. This publication was funded by Danone; however, they had no editorial control or say on the clinical input of this publication, and this was at the discretion of Mardeno Atlases and Morris Gordon. There are no other interests to declare.

Elena Biagioli - none known.

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