Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Review)

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[Intervention Review]

Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants

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ABSTRACT

Background

Allergies and food reactions are common and may be associated with foods including adapted cow's milk formula. Formulas containing hydrolysed proteins have been used to treat infants with allergy or food intolerance. However, it is unclear whether hydrolysed formula can be advocated for prevention of allergy and food intolerance in infants without evidence of allergy or food intolerance.

Objectives

To determine the effect of feeding hydrolysed formulas on allergy and food intolerance in infants and children compared to adapted cow's milk or human breast milk. If hydrolysed formulas are effective, to determine what type of hydrolysed formula is most effective including extensively and partially hydrolysed formulas. To determine which infants benefit, including infants at low or high risk of allergy and infants receiving early, short term or prolonged formula feeding.

Search strategy

The standard search strategy of the Cochrane Neonatal Review Group was used. The review was updated with searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE (1966 - March 2006), EMBASE (1980 - March 2006) and CINAHL (1982 - March 2006) and previous reviews including cross references.

Selection criteria

Randomised and quasi-randomised trials that compare the use of a hydrolysed infant formula to human milk or cow's milk formula. Trials with >80% follow up of participants were eligible for inclusion.

Data collection and analysis

Eligibility of studies for inclusion, methodological quality and data extraction were assessed independently by each review author. Primary outcomes included clinical allergy, specific allergies and food intolerance. Meta-analysis was conducted using a fixed effects model.

Main results

Two trials compared early, short term hydrolysed formula to human milk feeding. No significant difference in infant allergy or childhood cow's milk allergy (CMA) were reported. No eligible trial compared prolonged hydrolysed formula to human milk feeding. Two trials compared early, short term hydrolysed formula to cow's milk formula feeding. No significant benefits were reported. One large quasi-random study reported a reduction in infant CMA of borderline significance in low risk infants (RR 0.62, 95% CI 0.38, 1.00).

Ten eligible studies compared prolonged feeding with hydrolysed formula versus cow's milk formula in high risk infants. Meta-analysis found a significant reduction in infant allergy (seven studies, 2514 infants; typical RR 0.79, 95% CI 0.66, 0.94), but not in the incidence of childhood allergy (two studies, 950 infants; typical RR 0.85, 95% CI 0.69, 1.05). There was no significant difference in infant eczema (eight studies, 2558 infants, typical RR 0.84, 95% CI 0.68, 1.04), childhood eczema incidence (two studies, 950 infants, typical RR 0.83, 95% CI 0.63, 1.10), childhood eczema prevalence (one study, 872 infants; RR 0.66, 95% CI 0.43, 1.02), or infant or childhood asthma, rhinitis and food allergy. One study reported a significant reduction in infants with CMA with confirmed atopy (RR 0.36, 95% CI 0.15, 0.89). Subgroup analysis of trials blinded to formula found no significant difference in infant allergy (four studies, 2156 infants; typical RR 0.87, 95% CI 0.69, 1.08) or childhood allergy incidence (one study, 872 infants; RR 0.91, 95% CI 0.73, 1.14). No eligible trial examined the effect of prolonged hydrolysed formula feeding on allergy beyond early childhood. There is evidence that preterm or low birthweight infants fed a hydrolysed preterm formula have significantly reduced weight gain, but not in other growth parameters (head circumference or length). Studies in term infants report no adverse effects on growth.

Subgroup analysis of trials of partially hydrolysed versus cow's milk formula found a significant reduction in infant allergy (six studies, 1391 infants; typical RR 0.79, 95% CI 0.65, 0.97) but not childhood allergy, or infant or childhood asthma, eczema or rhinitis. Methodological concerns were the same as for the overall analysis. Analysis of trials of extensively hydrolysed formula versus cow's milk formula found no significant differences in allergy or food intolerance. Infants fed extensively hydrolysed formula compared with partially hydrolysed formula had a significant reduction in food allergy (two studies, 341 infants; typical RR 0.43, 95% CI 0.19, 0.99), but there was no significant difference in all allergy or any other specific allergy incidence. Comparing extensively hydrolysed casein containing formula with cow's milk formula, one study (431 infants) reported a significant reduction in childhood allergy incidence (RR 0.72, 95% CI 0.53, 0.97). Meta-analysis found a significant reduction in infant eczema (three studies, 1237 infants; typical RR 0.71, 95% CI 0.51, 0.97). One study reported a significant reduction in childhood eczema incidence (RR 0.66, 95% CI 0.44, 0.98) and prevalence (RR 0.50, 95% CI 0.27, 0.92).

Authors' conclusions

There is no evidence to support feeding with a hydrolysed formula for the prevention of allergy compared to exclusive breast feeding. In high risk infants who are unable to be completely breast fed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant CMA. In view of methodological concerns and inconsistency of findings, further large, well designed trials comparing formulas containing partially hydrolysed whey, or extensively hydrolysed casein to cow's milk formulas are needed.

PLAIN LANGUAGE SUMMARY

Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants

When babies are not exclusively breastfed, use of hydrolysed infant formula instead of ordinary cow's milk formula may reduce allergies in babies and children, although further studies are needed to confirm this. Infant formulas have been designed to try to lower the chances of developing allergy or food intolerance. These include hydrolysed cow's and soy milk formulas. Hydrolysed formulas break down the milk proteins into smaller, potentially less allergy producing proteins. The review of trials found that there is no evidence to support feeding with a hydrolysed formula to prevent allergy in preference to exclusive breastfeeding. In infants at high risk for allergy who are unable to be completely breastfed, there is limited evidence that feeding with a hydrolysed formula compared to a cow's milk formula reduces allergies in babies and children, including cow's milk allergy. Concerns regarding quality of the evidence and consistency of the results indicates further studies are needed.

BACKGROUND

An allergy is a specific reaction to a normally harmless substance (allergen) characterised by a specific IgE response. Common allergies include allergic rhinitis or hay fever, asthma, eczema or atopic dermatitis and food allergies. Allergies affect more than 20 percent of people (Austin 1999; Kuehni 2001; Habbick 1999; Manfreda 2001; Mortz 2001; Ronmark 2001; Sly 1999; Tariq 1998), and the prevalence of allergic diseases may be increasing (Downs 2001; Huovinen 1999; Kuehni 2001; Sly 1999). Many childhood allergies persist to adulthood with approximately 50% of childhood asthma sufferers (Barbee 1998; Sears 1998; Strachan 1996) and 80% of hay fever sufferers (Greisner 1998) continuing to have symptoms. Persistent symptoms were reported in 25 - 50% of childhood eczema sufferers at 16 years (Williams 1998) and 45% of 10 year olds who had cow's milk allergy (CMA) in infancy (Tikkanen 2000).

Many infants with atopy do not have a family history of atopy (Bergmann 1994; Sears 1996; Tariq 1998). However, the risk of atopy is increased to about one in three if one first-degree relative (parent or sibling) is atopic, and 70% if both parents are atopic (Bergmann 1994; Bergmann 1998; Ronmark 2001; Sears 1996; Tariq 1998). The predictive value of family history is increased with the addition of cord blood IgE antibody testing, although its accuracy may not be adequate for population screening (Bergmann 1997; Bergmann 1998; Tariq 1998). An increased duration of exclusive breast feeding has been associated with a reduced incidence of childhood allergy (Gruskay 1982; Oddy 1999; Saarinen 1995; Saarinen 2000), although not all studies support this association particularly with adult allergy (Sears 2002; Wright 2001). However, many infants are not exclusively breast fed (UNICEF). As a result, infants may receive either short or long term supplementary or sole feeding with an infant formula (usually adapted cow's milk or soy milk), or be weaned from the breast to formula.

The term 'food intolerance' does not imply a specific mechanism but is defined as a reproducible adverse reaction to a specific food or food ingredient. Mechanisms for food intolerance may comprise enzyme defects, pharmacological effects, irritant effects, and toxic reactions (David 2000; Host 1994; Host 1995). Food intolerance is diagnosed by resolution of typical symptoms with elimination from the diet, with confirmation by blinded challenge. Around 2 - 3% of babies develop an intolerance to a particular food. The principle symptoms in infants with proven cow's milk protein intolerance (CMPI) are gastrointestinal (~ 50%), dermatological (~ 31%) and respiratory (~ 19%) (Host 1994; Host 1995; Schrander 1993). Two in every three infants with CMPI have a family history of atopy (Schrander 1993). CMPI is strongly associated with feeding an adapted cow's milk formula to infants in the first month of life (Host 1991). Many infants with CMPI become tolerant over time with approximately 30% at one year, 50% at two years and 70% at three years tolerant to cow's milk challenge. The risk of persisting intolerance is increased with evidence of atopy (Host 1995; Carroccio 2000b).

A diagnosis of allergy may be made either by questionnaire, clinician assessment and confirmed by specific skin or serological testing, or by allergen challenge. The diagnostic criteria for different atopic conditions are not uniform and the mode of ascertainment of atopy is variable. Although tests of bronchial hyperresponsiveness, challenge tests and classical tests of IgE mediated hypersensitivity have an imperfect correlation with allergy symptoms and clinical signs (Darsow 2000; Peat 2000), they are associated with an increased likelihood of allergy and significant disease (Ronmark 2001; Sears 1998; Sly 1999; Strachan 1996). In addition, there is some evidence that questionnaires, although compromised by selection and recall bias (Peat 2001), are suitable for allergy screening (Kilpelainen 2001; Ravault 2001). This review includes trials that diagnose allergy either by questionnaire or clinician assessment, with or without confirmation by laboratory testing.

Measures to prevent allergy and food intolerance have included maternal allergen avoidance during pregnancy (Custovic 2000; Kramer 2001; Zeiger 1989) and/or lactation (Custovic 2000; Zeiger 1989), periods of exclusive breast feeding (Custovic 2000; Gruskay 1982; Oddy 1999; Saarinen 1995; Saarinen 2000), and avoidance of potential allergens including food and environment antigens in the first year of life and beyond (Custovic 2000). Formulas prescribed to infants with the intention of preventing allergy and food intolerance include hydrolysed cow's milk, elemental formulas, and adapted soy or hydrolysed soy formulas. Hydrolysed formulas are designed to change the allergenic milk protein with the aim of preventing sensitisation or intolerance. They may be produced from cow's milk or soy milk, be derived from predominately whey or casein proteins and be partially or extensively hydrolysed. The aim of this review is to determine the evidence for the use of hydrolysed infant formulas for prevention of allergy and food intolerance. This review does not include treatment of infants with clinically recognised allergy or food intolerance.

OBJECTIVES

To determine the effect of hydrolysed formulas for infant feeding on allergy and food intolerance. If hydrolysed formulas are effective, to determine what type of hydrolysed formula is most effective including extensively and partially hydrolysed formulas. To determine which infants are likely to benefit including infants at low or high risk of allergy and infants receiving early, short term or prolonged supplemental or sole formula feeding.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised trials that compare the use of a hydrolysed infant formula to human milk or an adapted cow's milk formula. Random and quasi-random (e.g. using alternation) trials with > = 80% follow up of participants were eligible for inclusion.

Types of participants

Infants in the first six months of life without clinical evidence of allergy.

Types of interventions

Hydrolysed infant formulas including:

- Hydrolysed cow's milk and soy formulas
- Extensively and partially hydrolysed formulas

Hydrolysed formulas may be used for either:

- Early, short term supplementary or sole formula feeding in infants unable to be exclusively breast fed in the first days of life
- Prolonged supplementation of breast fed infants or sole formula feeding in infants in the first months of life
- Weaning from the breast using infant formula

The control group may include infants who receive:

- Exclusive human milk (either breast fed or expressed)
- An adapted cow's milk formula

The following comparisons were prespecified:
1. Early short term hydrolysed formula versus human milk.
2. Prolonged use of a hydrolysed formula versus human milk.
3. Early short term hydrolysed formula versus cow's milk formula.
4. Prolonged use of a hydrolysed formula versus cow's milk formula.
Subgroup analyses included (see methods for definitions):
1. According to infant risk of allergy or food intolerance:

- Low risk infants (no family history allergy or food intolerance in 1^{st} degree relatives);
- High risk infants (family history allergy or food intolerance in 1^{st} degree relatives or high cord IgE level).

2. According to extent of protein hydrolysis:

- Extensively hydrolysed formula versus cow's milk formula;
- Partially hydrolysed formula versus cow's milk formula;
- Extensively hydrolysed formula versus partially hydrolysed formula.

3. According to indication for use:

- Prolonged sole formula feeding,
- Supplemental feeding or for weaning from the breast using infant formula.

4. According to method of ascertainment of allergy:

- Allergy / food intolerance confirmed by test.
- Blinded measurement for allergy or food intolerance.

5. According to type of protein hydrolysate used:

- Partially hydrolysed whey formula versus cow's milk formula.
- Partially hydrolysed casein formula versus cow's milk formula.
- Extensively hydrolysed whey formula versus cow's milk formula.
- Extensively hydrolysed casein formula versus cow's milk formula.
- Hydrolysed soy formula versus cow's milk formula.

Studies that included other allergy prevention interventions (e.g. maternal dietary avoidance measures, environmental allergy reduction measures) in the treatment and not the control group were excluded. Studies that had other allergy prevention interventions in both treatment and control groups were eligible.

Types of outcome measures

Primary outcomes:

- All allergy including asthma, atopic dermatitis, allergic rhinitis or food allergy
- Food intolerance

Secondary outcomes:

- Asthma
- Atopic dermatitis / eczema
- Allergic rhinitis
- Cow's milk or soy protein intolerance
- Cow's milk or soy protein allergy
- Food allergy
- Food intolerance
- Urticaria
- Anaphylaxis

Potential harms:

- Growth parameters including head circumference and weight gain
- Cost
- Infant feed refusal

A specific allergy or food intolerance may be diagnosed on the basis of:

- History of recurrent and persistent symptoms typical of the allergy or food intolerance
- Clinician diagnosis of allergy or food intolerance
- Clinical allergy and food intolerance confirmed by testing includes detection of allergen sensitisation by either skin testing or serological testing for specific IgE (e.g. RAST or EAST), asthma confirmed by respiratory function testing for presence of bronchial hyperresponsiveness and food intolerance confirmed by elimination/challenge.

The following definitions of age of allergy were used:

- Infant allergy incidence: allergy occurring up to two years of age.
- Childhood allergy incidence: allergy occurring up to 10 years of age (or up to age of latest report between two and 10 years).
- Childhood allergy prevalence: allergy reported that was present between two and 10 years of age.
- Adolescent allergy: allergy present from 10 to 18 years age.
- Adult allergy: allergy present after 18 years age.

Search methods for identification of studies

See: Collaborative Review Group search strategy.
The standard search strategy of the Cochrane Neonatal Review Group was used. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2003), MEDLINE (1966 - January 2003), EMBASE (1980 - January 2003) and CINAHL (1982 - January 2003) and previous reviews including cross references (all articles referenced), previous reviews including cross references, abstracts, conferences (Pediatric Academic Societies 1998-2002 and Perinatal Society of Australia and New Zealand 1998-2003), and journal hand searching mainly in the English language.
The search was updated March 2006 with additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE (1966 - March 2006), EMBASE (1980 - March 2006) and CINAHL (1982 - March 2006) and previous reviews including cross references (all articles referenced), previous reviews including cross references, abstracts, conferences (Pediatric Academic Societies 2003 - 2005 and Perinatal Society of Australia and New Zealand 2004 - 2005).
The search strategy included the following keywords, using the search fields of abstract, MeSH subject headings, exploded subject heading, publication type, subject heading word, text word, and title: A search on all fields for [infant* OR newborn* OR neonat* OR pediatric* OR paediatric*] AND [feed* OR food OR formula* OR hydrolysed* OR allergies OR diet* OR protein OR milk*] was conducted. The search was limited to: [random* OR trial* OR comparative study OR controlled study].

Data collection and analysis

This review updates a previous version Osborn 2003.
Eligibility of studies for inclusion were assessed independently by each review author. Only studies with > = 80% reporting of randomised infants were included. The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the trials included was evaluated regarding adequacy of randomisation and allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised individuals. A data collection form was used to aid extraction of relevant information and data from each included study. Each review author extracted the data separately. Data were compared and differences resolved by consensus. The standard methods of the Neonatal Review Group were used to synthesise the data. Effects are expressed as relative risk (RR), risk difference (RD) and 95% confidence intervals (CI) for categorical data, and weighted mean difference (WMD) and 95% CI for continuous data. Data were examined for heterogeneity using the chi-square test for heterogeneity. Heterogeneity was quantified using the I^2 statistic. The fixed effect model was used for meta-analysis where enrolled infants and interventions were similar and no significant heterogeneity was found. Sources of heterogeneity were explored in subgroup analysis.
Where the term 'hydrolysed formula' is used without a reference to type, this refers to both extensively and partially hydrolysed formulas. Studies that used hydrolysed formula for early (first few days of life) supplemental or sole infant feeding were not pooled with studies that used hydrolysed formula for prolonged feeding. All comparisons were performed including only studies with no different co-interventions prescribed for the prevention of allergy in either study arm (e.g. in treatment and not control group). Allergy preventing co-interventions included modifications to mothers diet when pregnant or breast feeding, or environmental modifications such as avoidance of pet hair and host dust mite reduction measures. Restricting analyses to studies with no differential co-interventions was not originally prespecified in the protocol.
Subgroup analyses were performed according to:
1. Infant risk of allergy or food intolerance: low risk infants (no family history allergy or food intolerance in 1st degree relatives); high risk infants (family history allergy or food intolerance in 1st degree relatives or high cord blood IgE level).
2. Extent of protein hydrolysis: extensively hydrolysed formula versus cow's milk formula; partially hydrolysed formula versus cow's milk formula; extensively hydrolysed formula versus partially hydrolysed formula. An extensively hydrolysed formula should meet the definition provided by the AAP Committee on Nutrition (AAP 2000) - the extensively hydrolysed proteins derived from cow's milk in which most of the nitrogen is in the form of free amino acids and peptides $\leq$ 1500 kDaltons, and should, at a minimum, ensure with 95% confidence that 90% of infants with documented CMA will not react with defined symptoms to the formula under

double-blind, placebo-controlled conditions.
3. Indication for use: prolonged sole formula feeding; supplemental formula feeding or weaning from the breast using infant formula.
4. Method of ascertainment of allergy or food intolerance: Clinical allergy confirmed by challenge testing or testing for atopy (e.g. skin testing or serological testing for specific IgE, asthma confirmed by testing for presence of bronchial hyperresponsiveness and food intolerance confirmed by elimination/challenge). Included in this definition is clinical allergy in a patient where atopy has been confirmed by testing (e.g. asthma where atopy has been confirmed by skin prick testing or RAST for specific IgE); blinded measurement for allergy or food intolerance - where measurement of outcome blinded to treatment allocation (this analysis was not prespecified).
5. Type of protein hydrolysate used: partially hydrolysed whey formula versus cow's milk formula; partially hydrolysed casein formula versus cow's milk formula; extensively hydrolysed whey formula versus cow's milk formula; extensively hydrolysed casein formula versus cow's milk formula; hydrolysed soy formula versus cow's milk formula.
Sensitivity analysis was performed for studies of adequate methodology defined as adequate randomisation and allocation concealment, and < 10% losses to follow up.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Ninety one articles or abstracts that compared types of interventions eligible for the review did not meet inclusion criteria for this review (see 'Characteristics of excluded studies' table). Several trials were excluded due to excess losses (Barberi 1993; Chan 2002; Decsi 1998; Fukushima 1997; Giovannini 1994; Halken 1992; Hill 2000b; Mihatsch 1999; Moran 1992; Odelram 1996; Raupp 1995; Schmelzle 2003; Schmitz 1992; Silva Rey 1996; Szajewska 2004; Zeiger 1989). Of these, Decsi 1998, Raupp 1995 and Schmitz 1992 did not report allergy. Twenty studies met criteria for inclusion (see Table 'Characteristics of included studies').
Types of infants enrolled:

- High risk: most studies (Chirico 1997; de Seta 1994; Halken 2000; Lam 1992; Mallet 1992; Marini 1996; Nentwich 2001; Oldaeus 1997; Tsai 1991; Vandenplas 1992; von Berg 2003; Willems 1993) enrolled infants at high risk of allergy on the basis of either a history of allergy in a first degree relative and/or a high cord IgE level. Lam 1992 did not report 'high risk' criteria.
- Risk not specified: studies that did not enrol infants on basis of perceived risk of allergy included: Juvonen 1996 enrolled healthy term infants although 62% had a family history of allergy; Maggio 2005 enrolled preterm infants ≤ 1750g and ≤ 34 weeks; Picaud 2001 enrolled infants < 1500g, ≤ 15 days; Saarinen 1999 enrolled healthy term infants requiring supplemental feeding in hospital; Szajewska 2001 enrolled low birthweight infants (< 2000g) with tolerance of full enteral feeds.
- Low risk: Vandenplas 1993 enrolled healthy term infants and excluded infants with a family history of allergy.

Types of interventions:
See 'Table of Included Studies' for types of formula used in each study.

1. EARLY SHORT TERM FEEDING OF HYDROLYSED FORMULA VERSUS HUMAN MILK FEEDING

Two studies (Juvonen 1996; Saarinen 1999) compared a hydrolysed formula with pasteurised donor human milk used for early infant feeding. Juvonen 1996 gave sole bottle feeds for three days then all infants were exclusively breast fed. Saarinen 1999 gave supplemental feeds when required while infants were in hospital (average four days). Mothers were then encouraged to breast feed.

2. PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS HUMAN MILK FEEDING

No study was found that compared prolonged hydrolysed formula feeding with human milk feeding (either breast or expressed).

3. EARLY SHORT TERM FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Two studies (Juvonen 1996; Saarinen 1999) compared a hydrolysed formula with an adapted cow's milk formula. Juvonen 1996 gave sole bottle feeds for three days then all infants were exclusively breast fed. Saarinen 1999 gave supplemental feeds when required while infants were in hospital (average four days). Mothers were then encouraged to breast feed.

4 PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Prolonged supplemental or sole feeding with a hydrolysed formula versus an adapted cow's milk formula without differential co-interventions was reported by 14 studies (Chirico 1997; de Seta 1994; Lam 1992; Maggio 2005; Mallet 1992; Marini 1996; Oldaeus 1997; Picaud 2001; Szajewska 2001; Tsai 1991; Vandenplas 1992; Vandenplas 1993; von Berg 2003; Willems 1993). Three studies (Chirico 1997; Marini 1996; Oldaeus 1997) reported additional allergy avoidance measures in both the hydrolysed formula and adapted cow's milk formula groups.

5. PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - LOW RISK INFANTS

One study (Vandenplas 1993) compared prolonged feeding with a hydrolysed formula with cow's milk formula in low risk infants but only reported infant growth.

6. PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - HIGH RISK INFANTS

Ten studies (Chirico 1997; de Seta 1994; Lam 1992; Mallet 1992;

Marini 1996; Oldaeus 1997; Tsai 1991; Vandenplas 1992; von Berg 2003; Willems 1993) compared prolonged feeding with a hydrolysed formula and a cow's milk formula in high risk infants.

7. PROLONGED FEEDING OF EXTENSIVELY HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Three studies (Mallet 1992; Oldaeus 1997; Szajewska 2001) compared prolonged feeding with an extensively hydrolysed formula with an adapted cow's milk formula.

8. PROLONGED FEEDING OF PARTIALLY HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Twelve studies (Chirico 1997; de Seta 1994; Lam 1992; Marini 1996; Oldaeus 1997; Picaud 2001; Szajewska 2001; Tsai 1991; Vandenplas 1992; Vandenplas 1993; von Berg 2003; Willems 1993) compared prolonged feeding with a partially hydrolysed formula with an adapted cow's milk formula.

9. PROLONGED FEEDING OF EXTENSIVELY HYDROLYSED FORMULA VERSUS PARTIALLY HYDROLYSED FORMULA

Four studies (Halken 2000; Nentwich 2001; Oldaeus 1997; Szajewska 2001) compared prolonged feeding with extensively hydrolysed formula with a partially hydrolysed formula.

10. PROLONGED SOLE FORMULA FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Prolonged sole formula feeding was reported by 10 studies (Chirico 1997; de Seta 1994; Lam 1992; Maggio 2005; Marini 1996; Picaud 2001; Szajewska 2001; Vandenplas 1992; Vandenplas 1993; Willems 1993) with six studies reporting allergy (Chirico 1997; de Seta 1994; Lam 1992; Marini 1996; Vandenplas 1993; Willems 1993).

11. PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - ALLERGY / FOOD INTOLERANCE CONFIRMED BY TEST

Three studies confirmed atopy or food intolerance in patients with clinical allergy by testing (Chirico 1997; Oldaeus 1997; Vandenplas 1992).

12. PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - BLINDED MEASUREMENT

Assessment for allergy without knowledge of patient allocation was reported by 11 studies (Halken 2000; Nentwich 2001; Oldaeus 1997; Saarinen 1999; Vandenplas 1992; Vandenplas 1993; von Berg 2003; Willems 1993).

13. PROLONGED FEEDING OF HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - STUDIES OF ADEQUATE METHODOLOGY

Maggio 2005; Oldaeus 1997; Szajewska 2001 and Tsai 1991 studied prolonged feeding of a hydrolysed formula compared to an adapted cow's milk formula with no co-interventions and are included in the sensitivity analysis of studies of adequate methodology (adequate randomisation and allocation concealment and < 10% losses to follow up).

14. PROLONGED FEEDING OF PARTIALLY HYDROLYSED WHEY FORMULA VERSUS COW'S MILK FORMULA

Ten studies (Chirico 1997; de Seta 1994; Lam 1992; Maggio 2005; Marini 1996; Picaud 2001; Tsai 1991; Vandenplas 1992; Vandenplas 1993; von Berg 2003) compared a partially hydrolysed whey formula to an adapted cow's milk formula.

15. PROLONGED FEEDING OF PARTIALLY HYDROLYSED CASEIN FORMULA CONTAINING FORMULA VERSUS COW'S MILK FORMULA

Two studies (Oldaeus 1997; Szajewska 2001) compared a partially hydrolysed formula containing casein to an adapted cow's milk formula.

16. PROLONGED FEEDING OF EXTENSIVELY HYDROLYSED WHEY FORMULA VERSUS COW'S MILK FORMULA

One study (von Berg 2003) compared an extensively hydrolysed whey formula to an adapted cow's milk formula.

17. PROLONGED FEEDING OF EXTENSIVELY HYDROLYSED CASEIN FORMULA CONTAINING FORMULA VERSUS COW'S MILK FORMULA

Four studies (Mallet 1992; Oldaeus 1997; Szajewska 2001; von Berg 2003) compared a extensively hydrolysed formula containing casein to an adapted cow's milk formula.

No study compared a hydrolysed soy formula to an adapted cow's milk formula.

No study compared a hydrolysed soy formula to a hydrolysed cow's milk formula.

Types of outcomes:

Most studies reported clinical allergy, atopy (specific IgE or skin prick tests) and challenge test results separately (i.e. atopy and challenge test results were not reported in infants with allergic symptoms as prespecified by this review). Therefore, the majority of outcomes reported in this review are for clinical allergy that was ascertained by questionnaire and / or physician assessment. Blinded (to study formula) clinician assessment for allergy was reported by Chirico 1997 at 6 months; Halken 2000 at six, 12 and 18 months; Nentwich 2001 at six and 12 months; Oldaeus 1997 at nine, 12 and 18 months; Saarinen 1999 to mean age 27 months; Vandenplas 1992 at 12 months; and von Berg 2003 at one and three years.

Studies that performed confirmatory testing for atopy included Chirico 1997 (RAST 6 months), Halken 2000 (unblinded food elimination / challenge), Juvonen 1996 (skin prick tests one and two years, total IgE), Mallet 1992 (RAST four and 12 months), Marini 1996 (RAST in first year and skin prick tests in second and third years), Nentwich 2001(specific IgE six and 12 months), Oldaeus 1997 (DBPCFC, skin prick tests, specific IgE at 18 months), Saarinen 1999 (unblinded cow's milk elimination / challenge), Tsai 1991 (specific IgE at two, six and 12 months, skin prick tests for infants with suspected CMA), Vandenplas 1992 (specific IgE, skin prick tests, unblinded food elimination / chal-

lenge to 12 months). In only three studies were allergy test results reported according to the presence of clinical symptoms of allergy or food intolerance (Chirico 1997; Oldaeus 1997; Vandenplas 1992). Definitions for allergy varied between studies but usually required persistent or recurring symptoms and signs in the absence of another obvious clinical explanation. For definitions of 'any allergy' and individual allergies for each study, see 'Characteristics of included studies'. Several studies did not report allergy but are included as they reported measures of growth in low allergy risk low birthweight infants (Maggio 2005; Picaud 2001; Szajewska 2001) and healthy low risk term infants (Vandenplas 1993) on a hydrolysed formula.

Risk of bias in included studies

Randomisation: Five studies reported an adequate method of randomisation (Chirico 1997; Maggio 2005; Oldaeus 1997; Picaud 2001; von Berg 2003). Eight studies reported random allocation of infants but not method of randomisation (de Seta 1994; Lam 1992; Mallet 1992; Marini 1996; Szajewska 2001; Tsai 1991; Vandenplas 1992; Vandenplas 1993). Five studies reported quasi-random methods of patient allocation including Halken 2000 (by date of birth), Juvonen 1996 (by day of month), Nentwich 2001 (odd and even numbers), Saarinen 1999 and Willems 1993 (month of birth).

Allocation concealment was probable for 10 studies (Chirico 1997; Maggio 2005; Marini 1996; Oldaeus 1997; Picaud 2001; Szajewska 2001; Tsai 1991; Vandenplas 1992; Vandenplas 1993; von Berg 2003). Allocation concealment was unclear for four studies including de Seta 1994 (method of allocation not reported), Halken 2000 (used quasi-random allocation method but blinded intervention), Mallet 1992 (method of allocation not reported) and Saarinen 1999 (quasi-random allocation method but blinded intervention). Studies with inadequate allocation concealment included Juvonen 1996 (quasi-random allocation, unblinded study), Lam 1992 (method not reported), Nentwich 2001 (quasi-random allocation, unblinded prescribing) and Willems 1993 (quasi-random allocation and unblinded study).

Blinding of treatment was reported by Chirico 1997; Halken 2000; Oldaeus 1997; Picaud 2001; Saarinen 1999; Szajewska 2001; Vandenplas 1992; Vandenplas 1993; von Berg 2003.

Blinding of measurement: physician assessment without knowledge of patient allocation was reported by eight studies (Halken 2000; Nentwich 2001; Oldaeus 1997; Saarinen 1999; Szajewska 2001; Vandenplas 1992; Vandenplas 1993; von Berg 2003). Blinding of measurement of allergy was reported by six studies (Halken 2000; Nentwich 2001; Oldaeus 1997; Saarinen 1999; Vandenplas 1992; von Berg 2003). Blinding of measurement of clinical allergy was not reported by eight studies (Chirico 1997; de Seta 1994; Juvonen 1996; Lam 1992; Maggio 2005; Picaud 2001; Tsai 1991; Willems 1993). Unblinded measurements were performed by Mallet 1992 and Marini 1996.

Losses to follow up: only studies with < 20% losses to follow up are included in this review. Studies with < 10% losses to follow up included de Seta 1994 (none reported), Lam 1992 (8%), Maggio 2005 (none), Mallet 1992 (7% at four months), Oldaeus 1997 (9%), Szajewska 2001 (none) and Vandenplas 1993 (9% but all in hydrolysed group). Saarinen 1999 followed up infants by mother self reporting and well baby clinic reporting. Infants with CMA maintained on a national register. Compliance rates are not reported.

Studies of adequate methodology as prespecified (adequate randomisation and allocation concealment and < 10% losses to follow up) included Maggio 2005, Oldaeus 1997, Szajewska 2001, Tsai 1991 and Vandenplas 1993 .

Effects of interventions

COMPARISON 01: EARLY SHORT TERM FEEDING: HYDROLYSED FORMULA VERSUS HUMAN MILK FEEDING - LOW RISK INFANTS

Two studies were included (Juvonen 1996; Saarinen 1999) that compared a short duration of early supplemental or sole hydrolysed formula versus donor human milk feeds in infants who were subsequently encouraged to breast feed. Juvonen 1996 (90 infants) reported no significant difference in any allergy (RR 1.43, 95% CI 0.38, 5.37), asthma (RR 0.48, 95% CI 0.05, 4.41), eczema (RR 0.48, 95% CI 0.05, 4.41), food allergy (RR 1.43, 95% CI 0.38, 5.37) and CMA (RR 7.11, 95% CI 0.35, 143.84) at three years. Saarinen 1999 (3559 infants) reported no significant difference in CMA up to mean age of 27 months (RR 0.87, 95% CI 0.52, 1.46).

The following subgroup analyses were considered, but as no significant benefits were reported, the results are not duplicated:

1. Both studies enrolled infants irrespective of family history allergy or food intolerance in 1st degree relatives.
2. Extent of protein hydrolysis: Juvonen 1996 and Saarinen 1999 compared an extensively hydrolysed formula versus pasteurised donor human milk.
3. Indication for use: both studies used formula for early short term infant formula feeding.
4. Method of ascertainment of allergy: Saarinen 1999 reported outcomes of an unblinded elimination / challenge for CMA. Juvonen 1996 did not report criteria for diagnosis of allergy.
5. Type of protein hydrolysate used: Juvonen 1996 compared an extensively hydrolysed casein formula versus pasteurised donor human milk. Saarinen 1999 compared an extensively hydrolysed whey formula versus pasteurised donor human milk.

Sensitivity analysis: neither study was considered to be of adequate methodology.

COMPARISON 02: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS HUMAN MILK FEEDING

No studies were eligible that compared these interventions.

COMPARISON 03: EARLY SHORT TERM FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Two studies (Juvonen 1996; Saarinen 1999) compared a short period of early supplemental or sole feeding with a hydrolysed formula with an adapted cow's milk formula. All mothers were subsequently encouraged to breast feed in both trials. Juvonen 1996 (77 infants) reported no significant difference in childhood allergy incidence (RR 1.37, 95% CI 0.33, 5.71), childhood asthma incidence (RR 3.08, 95% CI 0.13, 73.26), childhood eczema incidence (RR 0.34, 95% CI 0.04, 3.15), childhood food allergy (RR 1.37, 95% CI 0.33, 5.71) and childhood CMA (5.13, 95% CI 0.25, 103.43). Saarinen 1999 (3478 infants) reported a reduction in infant CMA of borderline significance (RR 0.62, 95% CI 0.38, 1.00; RD -0.01, 95% CI -0.02, 0.00).

The following subgroup analyses were considered, but as no significant benefits were reported, the results are not duplicated:

1. Both studies enrolled infants irrespective of family history allergy or food intolerance in 1st degree relatives.
2. Extent of protein hydrolysis: Juvonen 1996 and Saarinen 1999 compared an extensively hydrolysed formula versus cow's milk formula.
3. Indication for use: both studies used formula for early short term infant formula feeding.
4. Method of ascertainment of allergy: Saarinen 1999 reported outcomes of an unblinded elimination / challenge for CMA. Juvonen 1996 did not report criteria for diagnosis of allergy.
5. Type of protein hydrolysate used: Juvonen 1996 compared an extensively hydrolysed casein formula versus cow's milk formula. Saarinen 1999 compared an extensively hydrolysed whey formula versus cow's milk formula.

Sensitivity analysis: neither study was considered to be of adequate methodology.

COMPARISON 04: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Ten studies compared prolonged hydrolysed formula to adapted cow's milk formula feeding without any other differential (in one group only) allergy preventative co-interventions. Seven studies reported all allergy, with two studies (Lam 1992; Vandenplas 1993) reporting a significant reduction in infant allergy and one (Marini 1996) reporting a significant reduction in childhood allergy incidence. Meta-analysis (seven studies, 2514 infants) found a significant reduction in infant allergy (typical RR 0.79, 95% CI 0.66, 0.94; RD -0.04, 95% CI -0.08, -0.01), and meta-analysis (two studies, 950 infants) found no significant difference in childhood allergy incidence (typical RR 0.85, 95% CI 0.69, 1.05).

Five studies reported asthma, with meta-analysis (four studies, 318 infants) finding no significant difference in infant asthma (typical RR 0.57, 95% CI 0.31, 1.04). Marini 1996 (78 infants) reported no significant difference in childhood asthma incidence (RR 0.38, 95% CI 0.08, 1.84). von Berg 2003 (872 infants) reported no significant difference in childhood asthma prevalence (RR 1.06, 95% CI 0.70, 1.61).

Eight studies reported eczema with no individual study reporting a significant reduction in eczema at any time. Meta-analysis (eight studies, 2558 infants) found no significant difference in infant eczema infancy (typical RR 0.84, 95% CI 0.68, 1.04). Meta-analysis (two studies, 950 infants) found no significant difference in childhood eczema incidence (typical RR 0.83, 95% CI 0.63, 1.10). von Berg 2003 (872 infants) reported no significant difference in childhood eczema prevalence (RR 0.66, 95% CI 0.43, 1.02).

Two studies reported rhinitis, with meta-analysis (256 infants) finding no significant difference in infant rhinitis (RR 0.52, 95% CI 0.14, 1.85). Marini 1996 (78 infants) reported no significant difference in childhood rhinitis incidence (RR 0.48, 95% CI 0.04, 5.03).

Oldaeus 1997 (141 infants) reported no significant difference in infant food allergy (RR 1.82, 95% CI 0.64, 5.16). Vandenplas 1992 (67 infants) reported a significant reduction in infant CMA (RR 0.36, 95% CI 0.15, 0.89).

The following subgroup analyses were performed:

COMPARISON 05: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - LOW RISK INFANTS

No eligible study reported allergy outcomes in infants at low risk of allergy. Outcomes for growth in preterm or low birthweight infants fed a preterm hydrolysed or preterm cow's milk formula are as for Comparison 04. All subsequent analyses for allergy outcomes are in high risk infants.

COMPARISON 06: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - HIGH RISK INFANTS

All seven studies comparing prolonged hydrolysed formula feeding to adapted cow's milk formula feeding without any other allergy preventative co-interventions enrolled infants at high risk of allergy. See Comparison 05 for outcomes.

COMPARISON 07: PROLONGED FEEDING: EXTENSIVELY HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Four studies (Mallet 1992; Oldaeus 1997; Szajewska 2001; von Berg 2003) compared an extensively hydrolysed formula with a cow's milk formula. No individual study reported a significant reduction in all allergy or any specific allergy or food intolerance. Meta-analysis (two studies, 1561 infants) found no significant difference in infant allergy (typical RR 0.87, 95% CI 0.68, 1.13). von Berg 2003 (651 infants) reported no significant difference in childhood allergy incidence (RR 0.89, 95% CI 0.71, 1.13). Oldaeus 1997 (96 infants) reported no significant difference in infant asthma (RR 0.61, 95% CI 0.18, 2.04). von Berg 2003 (661 infants) reported no significant difference in childhood asthma prevalence (RR 1.02, 95% CI 0.65, 1.59). Meta-analysis (three studies, 1726 infants) found no significant difference in infant eczema (typical RR 0.83, 95% CI 0.63, 1.08). von Berg 2003 (661

infants) reported no significant difference in childhood eczema incidence (RR 0.86, 95% CI 0.63, 1.17) or prevalence (RR 0.64, 95% CI 0.40, 1.02). Oldaeus 1997 (96 infants) reported no significant difference in infant rhinitis incidence (RR 2.76, 95% CI 0.12, 66.22) and food allergy (RR 1.15, 95% CI 0.33, 4.02). Szajewska 2001, in 30 low birth weight infants at low risk of allergy, reported no significant difference in weight gain over the first 12 weeks (MD weight gain -2.02 g/day, 95% CI -5.76, 1.72).

COMPARISON 08: PROLONGED FEEDING: PARTIALLY HYDROLYSED VERSUS COW'S MILK FORMULA

Two studies (Lam 1992; Vandenplas 1992) independently reported a significant reduction in any infant allergy. Meta-analysis (seven studies, 1482 infants) found a significant reduction in any infant allergy (typical RR 0.79, 95% CI 0.65, 0.97). Meta-analysis of two studies (Marini 1996; von Berg 2003) found no significant difference in childhood allergy incidence (typical RR 0.86, 95% CI 0.67, 1.10). There was significant (p = 0.04) and substantial (I^2 = 75.2%) heterogeneity between studies, with Marini 1996 reporting a significant reduction (RR 0.42, 95% CI 0.19, 0.90) and von Berg 2003 no significant difference (RR 0.95, 95% CI 0.73, 1.25).

Meta-analysis (four studies, 268 infants) found no significant difference in infant asthma (typical RR 0.54, 95% CI 0.28, 1.04). Marini 1996 (78 infants) reported no significant difference in childhood asthma incidence (RR 0.38, 95% CI 0.08, 1.84) and von Berg 2003 (432 infants) reported no significant difference in childhood asthma prevalence (RR 1.15, 95% CI 0.70, 1.88). Meta-analysis (seven studies, 1361 infants) found no significant difference in infant eczema (typical RR 0.89, 95% CI 0.69, 1.13). Meta-analysis (two studies, 500 infants) found no significant difference in childhood eczema incidence (typical RR 0.85, 95% CI 0.61, 1.19) and von Berg 2003 reported no significant difference in childhood eczema prevalence (RR 0.71, 95% CI 0.41, 1.22). Meta-analysis (three studies, 206 infants) found no significant difference in infant rhinitis (typical RR 0.40, 95% CI 0.09, 1.70). Marini 1996 (78 infants) reported no significant difference in childhood rhinitis incidence (RR 0.48, 95% CI 0.04, 5.03). Oldaeus 1997 (91 infants) reported no significant difference in infant food allergy (RR 2.56, 95% CI 0.86, 7.56). Vandenplas 1992 reported a significant reduction in CMA in infancy (RR 0.36, 95% CI 0.15, 0.89).

Meta-analysis (two studies, 46 infants) in low birth weight or preterm infants fed a partially hydrolysed preterm infant formula versus a preterm infant cow's milk formula found no significant difference in weight gain (WMD -1.15 g/kg/day, 95% CI -2.90, 0.60).

COMPARISON 09: PROLONGED FEEDING: EXTENSIVELY HYDROLYSED FORMULA VERSUS PARTIALLY HYDROLYSED FORMULA

Four studies (Halken 2000; Nentwich 2001; Oldaeus 1997; von Berg 2003) compared prolonged feeding with an extensively hydrolysed formula to a partially hydrolysed formula in infants at high risk of allergy. No individual study reported any significant differences in allergy or food intolerance incidence. Meta-analysis (three studies, 1806 infants) found no significant difference in infant allergy (typical RR 0.93, 95% CI 0.75, 1.16). von Berg 2003 (661 infants) reported no significant difference in childhood allergy incidence (RR 0.93, 95% CI 0.74, 1.18).

Meta-analysis (two studies, 341 infants) found no significant difference in infant asthma incidence (typical RR 1.72, 95% CI 0.74, 3.96). von Berg 2003 (661 infants) reported no significant difference in childhood asthma prevalence (RR 0.89, 95% CI 0.58, 1.35). Meta-analysis (four studies, 1865 infants) found no significant difference in infant eczema (typical RR 0.89, 95% CI 0.73, 1.10). von Berg 2003 (661 infants) reported no significant difference in childhood eczema incidence (RR 0.92, 95% CI 0.69, 1.26) and prevalence (RR 0.90, 95% CI 0.54, 1.52). Meta-analysis of (two studies, 341 infants) found no significant difference in infant rhinitis (typical RR 1.25, 95% CI 0.36, 4.29). Meta-analysis of the same two studies (Halken 2000; Oldaeus 1997) found a significant reduction in infant food allergy (typical RR 0.43, 95% CI 0.19, 0.99). Halken 2000 (246 infants) reported no significant difference in infant CMA (RR 0.13, 95% CI 0.01, 1.16).

One study compared use of an extensively hydrolysed preterm formula with a partially hydrolysed preterm formula (Szajewska 2001) in 30 low birth weight infants at low risk of allergy, and reported no significant difference in weight gain over the first 12 weeks (MD weight gain -0.70 g/day, 95% CI -4.57, 3.17).

COMPARISON 10: PROLONGED SOLE FORMULA FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA

Six studies enrolled infants on sole formula feeds. Vandenplas 1992 reported a significant reduction in any infant allergy (RR 0.45, 95% CI 0.22 0.94). Meta-analysis (five studies, 425 infants) found a significant reduction in infant allergy (typical RR 0.61, 95% CI 0.46, 0.80). Marini 1996 reported a significant reduction in childhood allergy incidence (RR 0.42, 95% CI 0.19, 0.90).

Meta-analysis (two studies, 144 infants) found no significant difference in infant asthma (typical RR 0.57, 95% CI 0.25, 1.31). Marini 1996 reported no significant difference in childhood asthma incidence (RR 0.38, 95% CI 0.08, 1.84).

Meta-analysis (four studies, 271 infants) found no significant difference in infant eczema (typical RR 0.74, 95% CI 0.45, 1.21). Marini 1996 (78 infants) reported no significant difference in childhood asthma incidence (RR 0.42, 95% CI 0.14, 1,26) and childhood rhinitis incidence (RR 0.48, 95% CI 0.04, 5.03). Vandenplas 1992 reported a significant reduction in infant CMA (RR 0.36, 95% CI 0.15, 0.89).

COMPARISON 11: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - ALLERGY / FOOD INTOLERANCE CONFIRMED BY TEST

Most studies documented clinical allergy and results of confirmatory testing for allergy or atopy separately. Of studies that confirmed atopy in patients with clinical allergy, Vandenplas 1992 re-

ported a significant reduction in infant atopy confirmed by specific IgE (RR 0.45, 95% CI 0.22, 0.94). There were no infants with atopic rhinitis in one study (Oldaeus 1997) or atopic eczema in another (Chirico 1997). Oldaeus 1997 (141 infants) reported no significant difference in infant food allergy confirmed by specific IgE (RR 1.82, 95% CI 0.64, 5.16). Vandenplas 1992 reported a significant reduction in infant CMA confirmed by specific IgE (RR 0.36, 95% CI 0.15, 0.89). Oldaeus 1997 reported no significant difference in infant food intolerance confirmed by DBPCFC (RR 0.48, 95% CI 0.07, 3.33).

COMPARISON 12: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - BLINDED MEASUREMENT

Assessment for allergy without knowledge of patient allocation was reported by 5 studies (Halken 2000; Nentwich 2001; Oldaeus 1997; Vandenplas 1992; von Berg 2003). Meta-analysis (three studies, 2156 infants) found no significant difference in infant allergy (typical RR 0.87, 95% CI 0.69, 1.08). von Berg 2003 (872 infants) reported no significant difference in childhood allergy incidence (RR 0.91, 95% CI 0.73, 1.14). Oldaeus 1997 (141 infants) reported no significant difference in infant asthma (RR 0.48, 95% CI 0.17, 1.42) and von Berg 2003 (872 infants) reported no significant difference in childhood asthma prevalence (RR 1.06, 95% CI 0.70, 1.61). Meta-analysis of three studies (2124 infants) found no significant difference in infant eczema (typical RR 0.88, 95% CI 0.69, 1.14). von Berg 2003 (872 infants) reported no significant difference in childhood eczema incidence (RR 0.88, 95% CI 0.66, 1.18) or prevalence (RR 0.66, 95% CI 0.43, 1.02). Oldaeus 1997 (141 infants) reported no significant difference in infant rhinitis (RR 1.47, 95% CI 0.06, 35.37) or infant food allergy (RR 1.82, 95% CI 0.64, 5.16). Vandenplas 1992 (67 infants) reported a significant reduction in infant CMA (RR 0.36, 95% CI 0.15, 0.89).

COMPARISON 13: PROLONGED FEEDING: HYDROLYSED FORMULA VERSUS COW'S MILK FORMULA - STUDIES OF ADEQUATE METHODOLOGY

Maggio 2005; Oldaeus 1997; Szajewska 2001 and Tsai 1991 studied prolonged feeding of a hydrolysed formula compared to an adapted cow's milk formula with no co-interventions and are included in the sensitivity analysis of studies of adequate methodology (adequate randomisation and allocation concealment and < 10% losses to follow up). Oldaeus 1997 (141 infants) reported no significant difference in infant allergy (RR 1.13, 95% CI 0.69, 1.85). Meta-analysis of two studies (Oldaeus 1997; Tsai 1991) with 174 infants found no significant difference in infant asthma (typical RR 0.56, 95% CI 0.23, 1,38), infant eczema (typical RR 1.06, 95% CI 0.68, 1.65) or infant rhinitis (typical RR 0.40, 95% CI 0.09, 1.70). Oldaeus 1997 reported no significant difference in infant food allergy (RR 1.82, 95% CI 0.64, 5.16).

Meta-analysis of two studies (Maggio 2005; Szajewska 2001) comparing preterm infant formulas found a significant reduction in weight gain (WMD weight gain -2.43 g/kg/day, 95% CI -4.53, -0.34) for infants on hydrolysed preterm infant formula.

COMPARISON 14: PROLONGED FEEDING: PARTIALLY HYDROLYSED WHEY FORMULA VERSUS COW'S MILK FORMULA

Meta-analysis (six studies, 1391 infants) found a significant reduction in infant allergy (typical RR 0.73, 95% CI 0.59, 0.90). Meta-analysis (two studies, 510 infants) found no significant difference in childhood allergy incidence (typical RR 0.68, 95% CI 0.31, 1.52). Significant (p = 0.04) and substantial (I^2 = 75.2%) heterogeneity was found. Meta-analysis (three studies, 177 infants) found no significant difference in infant asthma (typical RR 0.61, 95% CI 0.29, 1.28). Marini 1996 (78 infants) reported no significant difference in childhood asthma incidence (typical RR 0.38, 95% CI 0.08, 1.84). von Berg 2003 (432 infants) reported no significant difference in childhood allergy prevalence (typical RR 1.15, 95% CI 0.70, 1.88). Meta-analysis (six studies, 1270 infants) found no significant difference in infant eczema (typical RR 0.84, 95% CI 0.65, 1.09). Meta-analysis (two studies, 510 infants) found no significant difference in childhood eczema incidence (typical RR 0.85, 95% CI 0.61, 1.19). von Berg 2003 (432 infants) reported no significant difference in childhood allergy incidence (typical RR 0.71, 95% CI 0.41, 1.22). Meta-analysis (2 studies 115 infants) found no significant difference in infant rhinitis (typical RR 0.4, 95% CI 0.09,1.70) and Marini 1996 reported no significant difference in childhood rhinitis incidence (typical RR 0.48, 95% CI 0.04,5.03). Vandenplas 1992 reported a significant reduction in infant CMA (RR 0.36, 95% CI 0.15, 0.89). Meta-analysis of two studies, 46 infants (Picaud 2001, Szajewska 2001) comparing preterm infant formulas found no significant difference in weight gain (WMD weight gain -1.15 g/kg/day, 95% CI -2.9, 0.60) for infants on hydrolysed preterm infant formula.

COMPARISON 15: PROLONGED FEEDING: PARTIALLY HYDROLYSED CASEIN CONTAINING FORMULA VERSUS COW'S MILK FORMULA

Oldaeus 1997 (91 infants) reported no significant difference in infant allergy (RR 1.36, 95% CI 0.80, 2.31), infant asthma (RR 0.34, 95% CI 0.07, 1.60), infant eczema (RR 1.30, 95% CI 0.66, 2.55) and infant food allergy (RR 2.56, 95% CI 0.86, 7.56). No infant was reported with rhinitis. Szajewska 2001 (30 infants) reported no significant difference in weight gain (MD weight gain -1.32 g/kg/day, 95% CI -4.83, 2.19) for infants on a partially hydrolysed casein containing preterm infant formula.

COMPARISON 16: PROLONGED FEEDING: EXTENSIVELY HYDROLYSED WHEY FORMULA VERSUS COW'S MILK FORMULA

von Berg 2003 (972 infants) reported no significant difference in infant allergy (RR 0.97, 95% CI 0.71, 1.34) and (431 infants) childhood allergy incidence (RR 1.07, 95% CI 0.82, 1.38). von Berg 2003 (431 infants) reported no significant difference in childhood asthma prevalence (RR 1.19, 95% CI 0.73, 1.94), infant eczema (972 infants, RR 1.00, 95% CI 0.72, 1.40), childhood eczema incidence (431 infants, RR 1.06, 95% CI 0.75, 1.49) and

childhood eczema prevalence (431 infants, RR 0.78, 95% CI 0.46, 1.33).

COMPARISON 17: PROLONGED FEEDING: EXTENSIVELY HYDROLYSED CASEIN CONTAINING FORMULA VERSUS COW'S MILK FORMULA

Meta-analysis (two studies, 1072 infants) found no significant difference in infant allergy (typical RR 0.79, 95% CI 0.58, 1.06). von Berg 2003 (431 infants) reported a significant reduction in childhood allergy incidence (RR 0.72, 95% CI 0.53, 0.97). Oldaeus 1997 (96 infants) reported no significant difference in infant asthma (RR 0.61, 95% CI 0.18, 2.04) and von Berg 2003 (431 infants) reported no significant difference in childhood asthma prevalence (RR 0.84, 95% CI 0.49, 1.45). Meta-analysis (three studies, 1237 infants) found a significant reduction in infant eczema (typical RR 0.71, 95% CI 0.51, 0.97). von Berg 2003 reported a significant reduction in childhood eczema incidence (RR 0.66, 95% CI 0.44, 0.98) and prevalence (RR 0.50, 95% CI 0.27, 0.92). Oldaeus 1997 (96 infants) reported no significant difference in infant rhinitis (RR 2.76, 95% CI 0.12, 66.22) and infant food allergy (RR 1.15, 95% CI 0,33, 4.02). Szajewska 2001 (30 infants) reported no significant difference in weight gain (MD weight gain -2.02 g/kg/day, 95% CI -5.76, -1.72) for infants on an extensively hydrolysed casein containing preterm infant formula.

ADVERSE EFFECTS OF HYDROLYSED FORMULAS

No study reported mortality or serious adverse events. No study reported neurodevelopment outcomes. All studies provided the infant formulas used in the study so data for the effect of infant formula cost on compliance is not available. No study reported a cost analysis of using a hydrolysed infant formula. Growth was reported by seven studies with four studies reporting growth in high risk infants (Mallet 1992; Marini 1996; Nentwich 2001; Tsai 1991) and five studies reporting growth in low risk infants (Maggio 2005; Picaud 2001; Szajewska 2001; Vandenplas 1993), with three of these studies (Maggio 2005; Picaud 2001; Szajewska 2001) enrolling low birthweight or preterm infants. Reports of growth and infant refusal of hydrolysed formula are summarised below.

- Growth:

Maggio 2005 reported growth in infants fed a preterm hydrolysed whey formula versus a preterm cow's milk formula that were isocaloric in protein, carbohydrate and fat. There was a significant reduction in weight gain in infants fed preterm hydrolysed whey infant formula (MD -3.10 g/kg/day, 95% CI -5.97, -0.23), but no significant difference in growth in head circumference (-0.06 cm/week, 95% CI -0.16, 0.94) or length (MD -0.02 cm/week, 95% CI -0.27, 0.23). The extent of hydrolysis was not reported.

Mallet 1992 reported a significantly reduced mean weight gain at four months but not 12 months in infants receiving an extensively hydrolysed formula compared to an adapted cow's milk formula (4 months: hydrolysed formula group 3060 g; adapted cow's milk formula 3290 g, $p < 0.05$). No difference in head circumference or length was found (data not given).

Marini 1996 reported no significant differences in weights or lengths at six months, one and three years or head circumferences at six months and one year for infants fed sole or supplemental partially hydrolysed formula versus adapted cow's milk formula.

Nentwich 2001 reported no significant difference in weights of infants (data not given) up to 12 months in infants fed a partially or extensively hydrolysed formula.

Picaud 2001 reported preterm infants fed a partially hydrolysed whey cow's milk formula were significantly lighter than infants fed an isocaloric adapted whey cow's milk formula (3193 +/- 384 g versus 3559 +/- 362 g, $p = 0.04$). The partially hydrolysed cow's milk formula had slightly lower nitrogen content.

Szajewska 2001 studied low birth weight infants at low risk of allergy and reported no significant difference in weight gain over the first 12 weeks comparing infants on a partially hydrolysed formula versus an adapted cow's milk formula (MD weight gain -2.02 g/day, 95% CI -5.76, 1.72), infants on an extensively hydrolysed formula compared to an adapted cow's milk formula (MD weight gain -0.70 g/day, 95% CI -4.57, 3.17) or infants on an extensively hydrolysed formula compared to a partially hydrolysed formula (MD weight gain -0.70 g/day, 95% CI -4.57, 3.17).

Tsai 1991 reported no significant difference in weight or height at 6 and 12 months in infants fed prolonged supplementary or sole hydrolysed formula versus a cow's milk formula (12 months weight: 9.91 kg SD 0.82 versus 9.74 kg SD 0.88; height 73.6 cm SD 3.7 versus 75.5 cm SD 4.0).

Vandenplas 1993 reported no significant difference in weight gain up to 13 weeks in healthy term infants fed prolonged sole 'intermediate' hydrolysed formula versus cow's milk formula (weight gain 27.2 g/day both groups).

- Infant refusal of hydrolysed formula:

No study prespecified that infant 'acceptance' or 'refusal' of a hydrolysed formula would be measured.

Nentwich 2001 at six months reported two 'dropouts' from the partially hydrolysed group due to "parental non-compliance' and one from the extensively hydrolysed formula group due to "poor acceptance of the hydrolysed formula".

Oldaeus 1997 reported "infant feeding problems" in three infants fed an extensively hydrolysed formula, six fed a partially hydrolysed formula and two fed an adapted cow's milk formula.

Vandenplas 1993 reported 4/25 infants fed an 'intermediate' hydrolysed formula with "refusal to drink" and 0/21 fed an adapted cow's milk formula.

DISCUSSION

Two trials compared a short period of early supplemental or sole hydrolysed formula to human milk feeding and found no significant reduction in infant allergy or CMA incidence up to childhood. No eligible trials were found that compared prolonged feeding with a hydrolysed formula to human milk feeds for the prevention of allergy or food intolerance. Until high quality trials are performed that compare prolonged hydrolysed formula feeding to breast or expressed human milk feeding, hydrolysed formula should not be routinely offered to infants for the prevention of allergy or food intolerance in preference to breast milk.

Meta-analysis of seven trials reporting 2514 infants found a significant reduction in infant allergy from use of a hydrolysed formula compared to a cow's milk formula in infants at high risk of allergy. Hydrolysed infant formula would need to be given to 25 infants (95% CI 12.5, 100) to prevent one infant developing allergy. This effect was no longer significant when allergy was measured after two years of age. These findings should be viewed with caution. Infant and childhood allergy had different definitions, timing of measurement and methods for measurement from study to study. Most studies were small or had methodological limitations with benefits not persisting when analysis was restricted to trials with blinding of measurement to study formula or to studies of adequate methodology. There was no significant difference in incidence of childhood allergy. Only one small study (Vandenplas 1992) reported a significant reduction in a specific allergy (CMA). Another trial (Oldaeus 1997) reported no significant difference in food allergy. There was no significant difference incidence of infant or childhood asthma, eczema or rhinitis. Several subgroup analyses were performed to determine if effects of hydrolysed formula varied according to intensity of exposure to cow's milk, method of allergy measurement and study quality.

Subgroup analysis of studies of sole formula feeding found a significant reduction in infant allergy (five studies, 425 infants), childhood allergy (one study, 78 infants) and infant CMA (one study, 67 infants), but no significant difference in infant or childhood asthma or eczema and childhood rhinitis. Subgroup analysis of studies where there was blinding to study formula for measurement of allergy and food intolerance, found no significant difference in infant or childhood allergy, asthma, eczema, rhinitis or food intolerance. Few studies reported testing for atopy using skin prick tests or specific IgE, food intolerance using DBPCFC, or bronchial hyperresponsiveness separately in infants with clinical symptoms of allergy or food intolerance. Tests were frequently performed on all enrolled infants and reported irrespective of symptomatology. This review focused on reports of probable or obvious allergy and food intolerance. Where atopy was confirmed by testing, the review focused on symptomatic infants only. Subgroup analysis of studies confirming allergy or food intolerance by testing, found only one study (Vandenplas 1992) reported a significant reduction in infant allergy and CMA. Subgroup analysis of studies of adequate methodology (adequate randomisation, allocation concealment and < 10% losses) found no significant difference in infant allergy, asthma, eczema, rhinitis or food allergy.

Further subgroup analyses were performed to determine if there were differences in effects between different types of hydrolysed formulas. Subgroup analysis comparing partially hydrolysed infant formulas with cow's milk formula found a significant reduction in infant allergy (six studies, 1391 infants), but no significant difference in childhood allergy (two studies, 510 infants), infant or childhood asthma, eczema or rhinitis. Vandenplas 1992 reported a reduction in infant CMA. Subgroup analysis comparing extensively hydrolysed infant formulas with partially hydrolysed formula found no significant difference in infant or childhood allergy, asthma or eczema, infant rhinitis or CMA. However, meta-analysis of two studies (Halken 2000; Oldaeus 1997) with 341 infants found a significant reduction in food allergy in infants receiving an extensively hydrolysed formula.

Additional subgroup analyses were performed to determine if there were differences in effects between different types of hydrolysed protein (100% whey or casein containing formulas). Most trials of partially hydrolysed formulas used partially hydrolysed 100% whey formula with analyses finding a significant reduction in infant allergy (six studies, 1391 infants), but no significant difference in childhood allergy (two studies, 510 infants), infant or childhood asthma, eczema or rhinitis. Again, Vandenplas 1992 was the only study to report CMA. Only one small trial (Oldaeus 1997) with 91 infants compared a partially hydrolysed casein formula with a cow's milk formula with no benefits reported. von Berg 2003 in 972 infants compared feeding with an extensively hydrolysed whey formula to a cow's milk formula and reported no significant difference in infant or child allergy and eczema, or childhood asthma. Three trials with 1237 infants compared feeding with an extensively hydrolysed casein containing formula to a cow's milk formula. One of these trials (von Berg 2003) reported a significant reduction in childhood allergy due largely to a reduction in infant and childhood eczema. Meta-analysis of two trials found no significant difference in infant allergy, but meta-analysis of three trials found a significant reduction in infant eczema. This finding is predominately due to the large von Berg 2003 study. These results should be viewed with caution given the losses to follow up at one and three years and the fact that no other eligible trial has demonstrated a significant benefit from use of an extensively hydrolysed formula. This large trial was conducted in a population of breast fed infants where formula was used as supplemental or sole formula feeding in those infants unable to fully breast feed. Under 60% of infants in the standard formula group were exposed to cow's milk formula, reducing the power of this study to detect an important difference in outcomes.

No trial without differential allergy preventing co-interventions reported use of a hydrolysed soy formula. Further trials are required to determine the role of hydrolysed soy formulas for allergy prevention in high risk infants.

Costs were not reported by any of the included studies. As the studies mostly provided the infant formulas, the effect of cost on compliance with treatment is not able to be determined. As no study prespecified or systematically measured infant acceptance of the formulas, the effect of formula on infant food refusal is not able to be determined. No study reported any adverse effect of hydrolysed formula on infant growth in term infants. However, there is consistent evidence that growth in weight, but not head circumference or length, of preterm or low birthweight infants fed a preterm hydrolysed formulas is significantly reduced. This is despite one study (Maggio 2005) comparing formulas that were isocaloric for protein, carbohydrate and fat. Whether this is of clinical importance is unclear given that formula intake can be adjusted according to growth parameters. None of the eligible studies reported neurodevelopmental or other health outcomes.

Given the limitations to the evidence supporting the use of hydrolysed formulas, further large well conducted trials with adequate randomisation procedures, blinding of intervention and complete follow up incorporating objective measures of allergy and food intolerance are needed. Given the findings of this review relating to potential benefits from partially hydrolysed 100% whey formulas and extensively hydrolysed casein formula, these trials should address the question of whether these formula types are better than cow's milk formula for prevention of allergy or food intolerance in high risk infants.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support feeding with a hydrolysed formula compared to exclusive breast feeding for the prevention of allergy or food intolerance. Until high quality trials are performed that compare prolonged hydrolysed formula feeding to breast or expressed human milk feeding, hydrolysed formula should not be routinely offered to infants for the prevention of allergy or food intolerance in preference to breast milk. There is no evidence of benefit from the use of a hydrolysed formula in preference to human milk for early, short term feeding in low risk infants. In infants at high risk of allergy who cannot be exclusively breast fed, there is limited evidence that prolonged supplementation with hydrolysed formula as opposed to cow's milk formula reduces the risk of allergy. However, there was no significant difference in rates of asthma, eczema or rhinitis. Effects on allergy did not persist in subgroup analysis of trials of adequate methodology or where allergy was proven with testing. There is limited evidence that use of a partially hydrolysed formula may prevent CMA, and that use of an extensively hydrolysed formula is better than a partially hydrolysed formula at preventing food allergy, although no differences were found for all allergy, asthma, eczema or rhinitis. There is limited evidence that use of an extensively hydrolysed casein formula prevents allergy, predominately eczema. Infant formulas were supplied by the researchers in the reported trials. The incremental costs of hydrolysed formulas and the effect of this cost if borne by the parents on compliance was not measured in any of the trials. A large, well conducted trial of hydrolysed formula compared to cow's milk formula is required before hydrolysed formulas is offered routinely in preference to other types of formula for prevention of allergy or food intolerance in high risk infants unable to solely breast feed.

Implications for research

Given that not all infants are able to be exclusively breast fed in the post partum period, a trial of supplemental hydrolysed formula feeding in infants at high risk of allergy requiring early supplemental feeding is warranted. Further trials are also needed in high risk infants requiring prolonged formula feeding. This is confirm the benefits reported from the use of a hydrolysed formula compared to a cow's milk formula, and to determine if the benefits persist to childhood, adolescence and adulthood. Further trials with adequate power are required in high risk infants to determine if there are any additional benefits from the use of an extensively hydrolysed formula in comparison to a partially hydrolysed formula for the prevention of allergy. Future trials should consider measuring the costs of providing hydrolysed formulas and, if these costs are to be borne by the parents, the effects of these costs on compliance. Trials should follow up all infants with an intention to treat analysis and measure clinical allergy as well as clinical allergy confirmed by testing.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chirico 1997

Methods	Adequate randomisation: yes, postnatal randomisation, sealed envelopes used. Allocation concealment: yes. Blinding of intervention: not reported. Blinding of measurement: yes for laboratory measurement, not reported for clinical allergy. Losses to follow up: unclear, numbers of enrolled infants not reported. Only infants who received 6 months of allocated formula analysed.
Participants	Infants of mothers with atopy (rhinitis, asthma, eczema or food intolerance)who "could not breast feed".
Interventions	1. (n = 21) Partially hydrolysed cow's milk whey formula (Vivena HA-Primigiorni HA). 2. (n = 14) Cow's milk formula (brand not reported). Co-interventions: (in all 'at risk infants') - avoidance of passive smoking, exposure to pets and mites, avoidance of nurseries and delayed weaning to 6 months age.
Outcomes	Primary outcome(s): immunogenicity and antigenicity of partially hydrolysed whey formula in at risk infants including RAST for milk and egg proteins, total and specific IgE and specific IgG and IgG4 subclass antibodies. Other outcomes: Eczema: pruritic, chronic or chronic relapsing dermatitis. Follow up to 6 months (infant eczema incidence).
Notes	Losses unclear. Groups unequal. Trial of sole, prolonged partially hydrolysed whey cow's milk formula and environmental allergen avoidance versus adapted cow's milk formula. Conflict of interest: none reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

de Seta 1994

Methods	Adequate randomisation: yes, postnatal randomisation of infants, method not reported. Allocation concealment: unclear. Blinding of intervention: not reported. Blinding of measurement: not reported. Losses to follow up: none reported.
Participants	Infants with at least one 1st degree relative with allergy. Where history in doubt, skin prick tests or RAST performed.

de Seta 1994 (*Continued*)

Interventions	1. (n = 23) Partially hydrolysed whey formula (Nidina-HA, Nestle). 2. (n = 39) Adapted cow's milk formula (Nidina, Nestle). Co-interventions: none reported. Formula only to 6 months, then 'normal' diet.
Outcomes	Primary outcome(s): allergic disease at 6 and 24 months (infant allergy). Other outcomes: physician clinical examination and/or telephone contact to determine incidence of allergic disease. CMPI, eczema and asthma diagnosed clinically according to standard criteria.
Notes	Trial of sole prolonged partially hydrolysed whey formula versus adapted cow's milk formula. Group sizes unequal. Conflict of interest: none reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Halken 2000

Methods	Adequate randomisation: no, quasi-random. Postnatal allocation by date of birth. Allocation concealment: unclear. Blinding of intervention: yes, used formula tins labelled 'A, B or C'. Blinding of measurement: yes. Losses to follow up: yes, unclear as to exact numbers in each group not completing study. Of inital population of 595 infants, 92% were included in study and 80% completed follow up. Reasons for losses included parental refusal (19), received other formula in 1st days (23), 'dropped out' (36), not seen at 18 months, did not fulfill inclusion criteria (4) and non-compliance (32).
Participants	Infants with biparental atopy or uniparental atopy and cord IgE>=0.3kU/l.
Interventions	Supplemental or sole formula feeding with: 1. (n = 79) Extensively hydrolysed casein formula (Nutramigen). 2. (n = 82) Extensively hydrolysed whey formula (Profylac). 3. (n = 85) Partially hydrolysed whey formula (NAN-HA). Recommended duration of feeding: 4 months. Co-interventions (all infants): delay solids and cow's milk to 4 months, avoid smoke, pets, damp housing.
Outcomes	Primary outcome(s): allergy. Other outcomes: physician examination at 6, 12 and 18 months (infant allergy). Definitions: Any atopy: symptoms of asthma, atopic dermatitis, allergic rhinoconjunctivitis or at least 2 episodes of allergic urticaria. Asthma: clinican diagnosed, >=3 episodes recurrent wheezing needing bronchodilators. Atopic dermatitis: physical examination. >= 3 months duration. Allergic rhinoconjunctivitis: >= 1 months or recurrent symptoms. Food allergy: confirmed by unblinded elimination/challenge.

	CMA/CMPI: confirmed by unblinded elimination / challenge, and exclusion of lactose intolerance and infection.
Notes	Trial of supplemental or sole partially hydrolysed whey formula versus extensively hydrolysed casein formula versus extensively hydrolysed whey formula in high risk infants. Control group of non-randomly allocated breast fed infants not included in analysis. Conflict of interest: funded by the Danish Dairy Foundation. Companies provided formula and funding.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Juvonen 1996

Methods	Adequate randomisation: no, quasi-random, infants allocated according to day of month. Allocation concealment: inadequate. Blinding of intervention: not reported. Blinding of measurement: not reported. Losses to follow up: yes, 14/130 lost for initial report (up to 4 months), 129 (90%) reported to 3 years.
Participants	144 healthy term infants of pregnant mother volunteers. 62% had family history of atopy.
Interventions	Early sole feeding for 3 days. Subsequently, all infants exclusively breast fed. 1. (n = 53) Pasteurised human milk feeds from milk bank. 2. (n = 38) Casein extensively hydrolysed formula (Nutramigen). 3. (n = 39) Cow's milk formula (Baby Semp).
Outcomes	Primary outcome(s): macromolecular absorption, antibody production and allergic symptoms. Other outcomes: serum IgE at 4 days, 8months, 1 and 2 years, skin prick test at 1 and 2 years, and clinical allergy to 3 years (child allergy incidence). Criteria for allergy diagnosis not reported.
Notes	Trial of early (1st 3 days) sole human milk versus adapted cow's milk formula versus extensively hydrolysed casein formula. Group numbers unequal. Use of volunteers meant possible selection of high risk infants. Conflict of interest: unclear, work supported by several foundations, affiliations not reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Lam 1992

Methods	Adequate randomisation: reported 'double blind randomisation', method not reported. Allocation concealment: unclear. Blinding of intervention: not reported. Blinding of measurement: not reported. Losses to follow up: yes, 8/100 (8%) - 6 in hydrolysed formula group and 2 in cow's milk formula group.
Participants	Infants not breast fed or stopped breast feeding in 1st 2 weeks. 'High risk infants' but criteria not reported.
Interventions	Allocated to either: Treatment (n=50): partially hydrolysed whey formula (Nan HA, Nestle), or Control (n=50): adapted cow's milk formula (Nan, Nestle). Co-interventions: none reported. Solids withheld for 6 months.
Outcomes	Primary outcome(s): allergic manifestations in 1st 6 months. Other outcomes: growth parameters in 1st 6 months. Definitions: Atopic symptoms included colic, respiratory atopy (wheeze and rhinitis) and skin atopy (eczema and urticaria). Eczema not defined.
Notes	Internal report of Nestle. Data not published. Numbers of infants with atopic manifestations at 6 months converted from percentages. Trial of prolonged feeding in infants at high risk of allergy with partially hydrolysed whey formula versus adapted cow's milk formula.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Maggio 2005

Methods	Adequate randomisation: yes, permutated blocks of 4, sealed in opaque envelopes, statified by gestation (<30 or >=30 weeks). Allocation concealment: yes. Blinding of intervention: yes, "identical in colour and smell", tins colour coded. Blinding of measurement: yes. Losses to follow up: none.
Participants	Preterm infants birthweight <=1750g and gestaton <=34 weeks. Not selected on basis of risk of atopy. Exclusions: major congenital malformations, intrauterine growth retardation, infection or major clinical problems.
Interventions	After establishing full enteral feeds, preterm infants randomly allocated to formula indentical in calories and protein, carbohydrate and fat content, either: Treatment (n=10): hydrolysed cow's milk derived 100% whey preterm formula (Humana GmbH, Herford Germany), or

Maggio 2005 (*Continued*)

	Control (n=11): cow's milk derived preterm formula with whey : casein ratio 51:49 (Humana GmbH, Herford Germany). Co-interventions. none.
Outcomes	Primary outcome(s): short term (4 weeks) growth and plasma and urinary amino acids. Other outcomes: Atopy not reported. Definitions: N/A.
Notes	Supported by Humana Italia S.p.A, Milano and Humana, Germany. Extent of formula hydrolysis not reported. Trial of prolonged feeding with partially hydrolysed cow's milk whey formula versus adapted cow's milk formula in preterm infants at low risk of allergy.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mallet 1992

Methods	Adequate randomisation: yes, infants randomised postnatally, method not reported. Allocation concealment: unclear. Blinding of intervention: no. Blinding of measurement: no. Losses to follow up: yes, hydrolysed formula group (n = 92): 5 (5%) at 4 months, 21 (23%) at 1 year, 14 (15%) at 2 years, 22 (24%) at 4 years. Cow's milk formula group (n = 85): 7 (8%) at 4 months, 32 (38%) at 1 year, 24 (28%) at 2 years and 31 (36%) at 4 years.
Participants	177 infants with immediate family history of allergy. Allergy score used.
Interventions	Sole or supplementary formula feeding for at least 4 months with: 1. (n = 92) Extensively hydrolysed casein formula (Pregestemil, Mead Johnson). 2. (n = 85) Adapted cow's milk formula (Galliazyme, Gallia, France). No co-interventions.
Outcomes	Primary outcome(s): allergy. Other outcomes: clinician assessment for allergy. Eczema and IgE assessed at 4 months, eczema, asthma and CMA assessed at 1, 2 and 4 years. Definitions: Atopic eczema: graded as mild (<4 patches), moderate or severe. Asthmatic bronchitis: grade 1 (2-4 occurences per year) and grade 2 (>4 per year). CMA: confirmed by type 1 reaginic allergy (specific IgE RAST) or malabsorption. Also reported weight at 4 months.
Notes	Excess losses at all time periods except 4 months (infant allergy incidence). Trial of supplemental or sole extensively hydolysed caasein formula versus adapted cow's milk formula.

Mallet 1992 (*Continued*)

	Only 4 months results included (infant allergy incidence). Conflict of interest: Mead Johnson and Gallia supplied formula.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Marini 1996

Methods	Adequate randomisation: yes, postnatal allocation of infants, method not reported. Allocation concealment: yes. Blinding of intervention: no. Blinding of measurement: no. Losses to follow up: yes, hydrolysed group losses 5 (10%) at 1 year, 6 (13%) at 2 years and 8 (17%) at 3 years. Cow's milk group 6 (13%) at 1 year, 7 (15%) at 2 years and 9 (19%) at 3 years.
Participants	Maternal questionnaire used to identify infants with well-defined family history of allergy in either parent.
Interventions	Infants randomised were those whose mothers did not wish to breastfeed or had insufficient milk. 1. (n = 48) 'Moderately' hydrolysed formula (Nidina HA, Nestle). 2. (n = 47) Adapted cow's milk formula (Nan, Nestle). Formula feeding advised to 5 months. Co-interventions (both groups): Maternal cow's milk and food avoidance measures for breastfeeding mothers. For infants, cow's milk and allergenic foods avoided to 1 year. Advice given to modify environmental exposure (smoking, pets, carpets, avoiding infant community care to 2 years).
Outcomes	Primary outcome(s): allergic manifestations and nutritional adequacy of formula. Other outcomes: weight, length and head circumference at 6 months, 1 and 3 years. Physician diagnosed allergy. Definitions: Atopic dermatitis: typical rash in at least 2 areas. Recurrent wheezing: >= 3 episodes and phsyician diagnosed. Recurrent urticaria: >=2 episodes after exposure to particular antigen. Gastrointestinal symptoms: vomiting and/or diarrhoea after exclusion of infection and lactose intolerance, not confirmed by blinded elimination/challenge Allergic rhinitis: >= 3 weeks rhinorrhoea. RAST and skin prick tests also performed in affected individuals. Follow up performed at 1, 2 (infant allergy) and 3 years (child allergy). Weight, length and head circumference measured at 6 months, 1 year and 3 years.
Notes	Trial of prolonged supplemental or sole 'moderately' hydrolysed whey formula versus adapted cow's milk formula feeding in high risk infants. Co-interventions in both groups. Conflict of interest: none reported.

Marini 1996 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Nentwich 2001

Methods	Adequate randomisation: no, quasi-random - prenatal randomisation by odd and even numbers. Allocation concealment: no, postnatal allocation to formula if unable to fully breast feed. Blinding of intervention: no, paediatrician prescribing treatment aware of allocation. Formula not blinded. Blinding of measurement: yes, second paediatrician unaware of allocation. Losses to follow up: yes, 1/73 (1%) post randomisation loss. 13/72 (18%) not fed hydrolysed formula and reported in separate group.
Participants	Pregnant women who themselves, husbands or children attended an allergology or dermatology outpatient clinic (ie family history of atopy in 1st degree relative).
Interventions	Mothers encouraged to breast feed for at least 6 months, avoid cow's milk and highly allergenic foods. Allocated sole or supplemental formula if unable to solely breast feed according to prenatal treatment allocation. 1. (n = 37) Partially hydrolysed whey cow's milk formula (Beba HA, Nestle, Denmark). 2. (n = 35) Extensively hydrolysed whey cow's milk formula (Hipp HA, Hipp GnbH, Gmunden, Austria). Co-interventions: all mothers encouraged to breast feed for 6 months, avoid cow's milk for first 6 months, introduce solids after 6 months and delay allergenic foods to after 12 months. At 6 months: 24/37 fed partially hydrolysed formula and 21/35 fed extensively hydrolysed formula. At 12 months, 31/37 fed partially hydrolysed formula and 28/35 extensively hydrolysed formula.
Outcomes	Primary outcome(s): Antigen-specific reactivity of mononuclear cells to cow's milk protein; cow's milk specific IgE and IgG; atopic skin symptoms. Other outcomes: symptom diaries kept. Blinded paediatrician assessment for atopic dermatitis. Reported weights up to 12 months (data not given). Definitions: Atopic dermatitis: typical rash in at least 2 locations relapsing for at least 3 months duration. Standardised score used (SCORAD). Allergy reported at 6 and 12 months (infant allergy).
Notes	Trial of sole or supplemental feeding partially hydrolysed whey formula versus extensively hydrolysed whey formula in high risk infants unable to be completely breast fed in first 6 months. Supported by research grants. The "study done independently of infant food companies".

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Oldaeus 1997

Methods	Adequate randomisation: yes, stratified by age at weaning. Infants randomised when weaning commenced. Allocation concealment: yes. Blinding of intervention: yes, identical coded tins used for extensively and partially hydrolysed formulas; no blinding of cow's milk formula tin. Blinding of measurement: yes. Losses to follow up: yes, 14/155 post randomisation losses (9%) at 18 months.
Participants	Term newborn infants with 2 allergic family members or one allergic family member and cord IgE >= 0.5U/l. Mean age of weaning between 3 and 4 months.
Interventions	In infants weaning from the breast: 1. (n = 55) Extensively hydrolysed casein formula (Nutramigen, Mead Johnson). 2. (n = 51) Partially hydrolysed formula whey : casein ratio 60:40 (Mead Johnson). 3. (n = 49) Cow's milk formula (Enfamil, Mead Johnson). Co-interventions: both groups advised to not smoke and avoid pets. Solids introduced after 4 months. Avoidance of cow's milk, eggs, fish and citrus to after 9 months.
Outcomes	Primary outcome(s): atopic and allergic disease at 18 months (infant allergy incidence). Other outcomes: nurse examination at 3, 6, 9, 12, 18 months and doctor visit at 18 months. Skin prick tests at each visit and specific IgE RAST at 9, 12, 18 months. Definitions: Atopic dermatitis: standard scoring system used. Food reactions: double blind placebo controlled challenges for formula milk reactions. Asthma: recurrent wheeze with doctor confirmation. Allergic rhinitis: doctor verified and allergen sensitisation proved. Gastrointestinal allergy: positive unblinded oral challenge to food infant sensitised to.
Notes	Trial of extensively hydrolysed versus partially hydrolysed versus cow's milk formula for weaning high risk infants. Conflict of interest: co-investigator from formula company. Formula supplied by Mead Johnson. Study supported by Bristol-Meyers inc.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Picaud 2001

Methods	Adequate randomisation: yes, method not reported, used opaque sealed envelopes. Allocation concealment: adequate. Blinding of intervention: yes. Blinding of measurement: not reported. Losses to follow up: yes, 2/18 (11%) withdrawn after randomisation.

Picaud 2001 (*Continued*)

Participants	Birthweight <1500g, age <=15days at start of enteral feeding and exclusive formula feeding. Not selected on basis of risk of atopy. Exclusion criteria: breast feeding, diabetic mother, intrauterine growth retardation, major congenital abnormality or infection or major clinical problem.
Interventions	Randomised to isocaloric trial formulas until term corrected age: Treatment (n=9): partially hydrolysed preterm whey formula (Nutrition Laboratory in Liege), Control (n=7); standard preterm cow's milk whey formula (Nutrition Laboratory in Liege). Co-interventions: none.
Outcomes	Primary outcome(s): nitrogen, amino acid and mineral balances. Other outcomes: Clinical tolerance and growth. Definitions: N/A.
Notes	Sponsored by Nestle Company (Switzerland and France). Partially hydrolysed formula had slightly lower nitrogen and higher calcium content. Trial of prolonged use of partially hydrolysed preterm whey formula versus preterm cow's milk formula in preterm infants.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Saarinen 1999

Methods	Three hospital study. Adequate randomisation: no, quasi-random allocation by month of birth and hospital born. Allocation concealment: unclear, possible if blinding maintained. Blinding of intervention: yes, colour coded bottles used. Blinding of measurement: yes. Losses to follow up: unclear. 6209/6267 (99%) of eligible mothers returned baseline questionnaire. Mothers were asked to call author if symptoms of CMA appeared. Compliance not assessed. Diary of infant-feeding regimen returned by 118/118 mothers of infants subsequently found to be hypersensitive to CM and 76% CM tolerant infants.
Participants	Healthy full term infants requiring supplemental feeding in hospital.
Interventions	Early supplementary feeding in hospital with: 1. (n = 1758) Cow's milk formula (Tutteli, Vali, Finland). 2. (n = 1844) Pasteurised donor human milk. 3. (n = 1715) Extensively hydrolysed whey formula (Pepti-Junior, Nutricia, Netherlands). Average duration hospital stay 4 days. Mothers encouraged to breast feed. Supplemental cow's milk formula used after discharge where required. Solids introduced at 4-6 months. No co-interventions.

Saarinen 1999 (*Continued*)

Outcomes	Primary outcome(s): CMA. Other outcomes: CMA - mothers contacted researchers if symptoms suggestive of CMA appeared. Well baby clinics also informed of study (all infants seen average 8 times in 1st 12 months). Definition: CMA: unblinded elimination / challenge performed. Mean age follow up 27 months (range 18-34 months) (infant allergy).
Notes	Trial of early supplemental human milk versus extensively hydrolysed whey formula versus cow's milk formula. Potential ascertainment bias as compliance with reporting not assessed. Conflict of interest: supported by Nutricia.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Szajewska 2001

Methods	Adequate randomisation: yes, method not reported. Allocation concealment: adequate. Blinding of intervention: yes, powdered formulas provided with identical packaging and reconstitution instructions. Blinding of measurement: yes. Losses to follow up: none.
Participants	Inclusion criteria: Low birthweight infants (<2000g), appropriate for gestational age, tolerance of at least 150mls/kg/day full enteral feeds, no obvious disease or congenital abnormality.
Interventions	Preterm infants fed preterm formula from tolerating full enteral feeds for 12 weeks. 1. (n = 16) Extensively hydrolysed preterm formula, whey : casein ratio 60:40 (Nutricia, Holland). Per 100 mls provided 2.4g protein and 522 kcal energy. 2. (n = 15) Partially hydrolysed preterm formula, whey : casein ratio 60:40 (Nutricia, Holland). Per 100 mls provided 2.5g protein and 527 kcal energy. 3. (n = 15) Standard preterm formula, whey : casein ratio 60:40 (Nutricia, Holland). Per 100 mls provided 2.2 g protein and 520 kcal energy. No co-interventions.
Outcomes	Primary outcomes: growth, indices of protein metabolism and plasma amino acid profiles in preterm infants followed for 3 months. Other outcomes: allergy not reported. Growth in weight, length and head circumference reported to 12 weeks. numerical data not given for growth in length or head circumference.
Notes	Trial of sole extensively hydrolysed whey/casein preterm formula versus partially hydrolysed whey casein preterm formula versus standard whey/casein preterm formula in preterm infants at low risk of allergy. Supported by research grant from Ovita Nutricia Research Foundation.

Szajewska 2001 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Tsai 1991

Methods	Adequate randomisation: yes, infants randomised postnatally, method not reported. Allocation concealment: adequate. Blinding of intervention: no, one group breastfed initially. Blinding of measurement: not reported. Losses to follow up: crossover of 3 infants from hydrolysed to cow's milk formula group (unclear which reported outcomes this affected).
Participants	Healthy term infants. Family History of Allergy Score used. Infants with score >3 enrolled.
Interventions	1. (n = 15) Infants breast fed for 1-2 months then fed partially hydrolysed formula for subsequent 4 months (Nan HA, Nestle). All except 2 infants received formula. 2. (n = 18) Regular formula from birth. No co-interventions reported.
Outcomes	Primary outcome(s): allergic diseases. Other outcomes: seen at 1, 2, 4, 6, 12 months (infant allergy incidence)in well baby clinic. Total and specific IgE at 2, 6, 12 months. Skin prick tests in cases of suspected allergy. Growth in weight and height up to 12 months. Definitions: Atopic dermatitis: grading score used (mild: faint lesions on forehead or cheek without treatment; moderate and severe: lesions required treatment). Allergic rhinitis: typical symptoms in early morning. Wheezing: any. Weights and height reported at 6 and 12 months.
Notes	Trial of prolonged supplementary or sole partially hydrolysed whey formula versus cow's milk formula. Data not reported in group of allocation for clinical allergy confirmed by skin prick testing, and possibly for growth. Conflict of interest: financial support and formula provided by ANPING Ltd.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Vandenplas 1992

Methods	Adequate randomisation: yes, infants postnatally allocated, method not reported. Allocation concealment: yes. Blinding of intervention: yes, formulas coded. Blinding of measurement: yes. Losses to follow up: yes, at 12 months 8/75 (11%) post randomisation losses. At 3 and 5 years, 17/75 (23%) lost to follow up.
Participants	Infants with at least two 1st degree relatives with allergy, whose mothers intended not to breast feed.
Interventions	Exclusive formula feeding for 6 months with: 1. (n = 32) Whey partially hydolysed whey formual (Nan HA, Nestle). 2. (n = 35) Adapted cow's milk formula (Nan, Nestle). Co-interventions (both groups): grated apple from 4 months. 'Normal' diet after 6 months.
Outcomes	Primary outcome(s): atopic disease. Other outcomes: Blinded physician assessment for allergy monthly for 1st year of life. Total IgE, specific RAST, IgG4 antibodies, and skin prick tests. Definitions: Atopic dermatitis: at least 3 of 4 criteria including typical rash, recurrence or chronicity and specific IgE. Urticaria: no definition given. Allergic wheezing: cough without infection >= 24 hours. Chronic rhinitis: clear nasal discharge. CMPI: confirmed by unblinded elimination / challenge. Allergic diarrhoea: infection excluded. Infants with diarrhoea had jejunal biopsy performed. Follow up to 12 months (infant allergy incidence).
Notes	Trial of prolonged sole partially hydrolysed whey formula versus cow's milk formula in high risk infants. 3 and 5 year results excluded due to excess losses. Data for cummulative specific allergy manifestations up to 12 months not extractable separately. Conflict of interest: Nestle provided formula and performed statistical analysis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Vandenplas 1993

Methods	Adequate randomisation: yes, infants postnatally allocated, method not reported. Allocation concealment: adequate. Blinding of intervention: yes, although formulas different appearance and taste. Blinding of measurement: yes. Losses to follow up: yes, 4/45 (9%) infants (all hydrolysed formula group) lost due to refusal to drink formula.
Participants	Healthy term newborn infants. Infants with family history of atopy excluded.

Vandenplas 1993 (*Continued*)

Interventions	Exclusive formula feeding for 13 weeks of: 1. (n = 21) Whey 'intermediate' hydrolysed formula (Nutrilon Pepti, Nutricia). 2. (n = 20) Whey predominant cow's milk formula (Nutrilon Premium, Nutricia). No co-interventions.
Outcomes	Primary outcome(s):nutritional value of formula. Other outcomes: weight gain (g/day) and length gain birth to week 13. Full blood count indices, serum protein, albumin, urea, calcium and phosphorous, minerals and vitamins A and E. Plasma amino acid concentrations. Clinical allergy not reported.
Notes	Trial of prolonged sole 'intermediate' hydrolysed whey formula versus whey cow's milk formula in healthy term infants. Growth data not extractable for tables. Included in text. Conflict of interest: Nutricia Belgium provided formula and assistance for statistical analysis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

von Berg 2003

Methods	Adequate randomisation: yes, computer generated list stratified for single or double parental atopy and study region. Allocation concealment: adequate. Blinding of intervention: yes, used identically labelled tins. Blinding of measurement: yes. Losses to follow up: yes. In the intention to treat analyses for all study centres (Munich and Wesel) that included breast fed infants: at 1 year 304/2252 (13.5%) and 3 years 692/2254 (31%). In intention to treat analyses for Wesel only that included breast fed infants at 1 year 158/1078 (14.7%) and 3 years 206/1078 (19%).
Participants	High risk of allergy healthy infants with at least one 1st degree family member with allergy. Exclusion criteria: severe aquired or congenital diseases, gestation <37 weeks, birth weight < 2500g, >14 days, intake cow's milk based formula before inclusion, incapability of parent to comply with study protocol.
Interventions	Mothers encouraged to breast feed for at least 4 months. Study formula provided for when sole breast feeding no longer continued and provided until infant 6 months age. Infants randomised to either: 1. Partially hydrolysed 100% whey formula (Beba HA, Nestle, Vevey, Switzerland); or 2. Extensively hydrolysed 100% whey formula (Hipp HA, Hipp, Pfaffenhofen, Germany), 3. Lactose-free, extensively hydrolysed 100% casein formula (Nutramigen, mead Johnson, Diezenbach, Germany), 4. Adapted cow's milk formula with casein : whey ratio 40:60 (Nutrilon Premium, Nutricia/Numico, Zoetermeer, Netherlands). Co-interventions: all groups received advice about breast feeding for at least 4 months, preferably 6, no

von Berg 2003 (*Continued*)

	dietry restrictions during lactation, not to feed solids during study period, thereafter to add one food a week and avoid common allergenic foods in 1st year. 58.4% of infants received study formula.
Outcomes	Primary outcome(s): allergy. Other outcomes: Allergy (atopic manifestations), asthma and eczema. Definitions: Allergy (atopic manifestations)diagnosed at 12 months (infant allergy) as atopic dermatitis, allergic urticaria or gastrointestinal food allergy. Atopic dermatitis: typical morphology and distribution of skin lesions; pruritus; chronicity (duration >=14 days, chronically relapsing, or both); confirmed on skin examination by a second specially trained allergologist; severity rated using the SCORAD method. Allergic urticaria: at least 2 episodes of itching eruptions or swelling with typical appearance, observed by the parents or a physician, were caused by the same allergen. In case of a single episode, immunologic evidence (specific skin prick test. or allergen-specific IgE level of >=0.35 KU/L or a positive provocation response). Gastrointestinal food allergy: suspected if gastrointestinal symptoms not explained by any other condition and if unblinded elimination challenge reproduced symptoms. Gastrointestinal allergy definite if a positive standardised elimination-challenge procedure. Double-blind, placebo-controlled food challenge performed in cases of uncertain reactions. At 3 years, childhood allergy included atopic dermatitis, urticaria, food allergy with manifestation in the gastrointestinal tract, and asthma. Allergic asthma: diagnosed from parental report of either relevant symptoms (wheeze and/or cough without infection)or regular use of asthma-medication in the child's 3rd year of life. Asthma symptoms included: 1. wheezing or cough for at least 2 weeks (acute laryngotracheitis excluded); 2. exercise-induced wheeze or cough at any time (with crying laughing or activity); 3. three episodes of either wheezing or dry nighttime cough.
Notes	Data of intention to treat analyses of all infants (including breast fed infants) according to study centre provided by study authors. Analyses meeting inclusion criteria for the review are the intention to treat analyses including breast fed infants for all study centres at 1 year and infants enrolled in Wesel for 3 year outcomes. Study supported by Federal Ministry for Education, Science, Research and Technoilogy and the Child Health Research Foundation. Formulas provided by Nestle, Hipp, Milupa, Numico, and Mead Johnson. Trial of prolonged breast feeding with supplemental or sole formula feeding when required comparing use of adapted cow's milk formula, partially hydrolysed whey formula, extensively hydrolysed whey formula and lactose free extensively hydrolysed casein formula.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Willems 1993

Methods	Adequate randomisation: no, quasi-random - infants postnatally allocated using month of birth. Allocation concealment: inadequate. Blinding of intervention: no. Blinding of measurement: no. Losses to follow up: yes, 17/135 (13%) of high risk infants did not complete study.
Participants	Infants not breast fed with a family history of allergy and cord IgE >=0.5IU/l.
Interventions	Prolonged sole formula feeding with: 1. (n = 55) Adapted cow's milk formula. 2. (n = 67) Partially hydrolysed whey formula (Nan HA). Formula used for 1st 3 months, then unrestricted diet. No co-interventions.
Outcomes	Primary outcome(s): allergy. Other outcomes: paediatrician administered questionnaire at 3 months and 1 year for allergy (infant allergy incidence). Definitions: Allergy included eczema, asthma, recurrent episodes of bronchitis, perstent rhinitis, persistent gastrointestinal symptoms (excluding infection)and sleeping difficulties. No specific definitions given.
Notes	High rate (45%) of non-compliance with formula. Trial of prolonged sole partially hydrolysed whey formula versus adapted cow's milk formula in high risk infants. Conflict of interest: unclear, co-investigator from FNRS, Brussels.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

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

Agosti 2003	Method of allocation not reported. Did not measure atopy.
Akimoto 1993	Cohort study.
Arshad 1992a	Had multiple allergy preventing co-interventions in treatment and not the control group.
Arshad 1992b	Cohort study.
Arshad 1993	Cohort study.

(*Continued*)

Arshad 2001	Cohort study.
Atherton 1978	Enrolled infants with atopic eczema.
Barberi 1993	Excess post randomisaton losses - 278/815 (34%).
Bellioni 1999	Enrolled infants with proven Ig-E mediated CMA.
Bergmann 1994	Cohort study.
Bergmann 1996a	No dietry intervention in infants. Compared high risk cases to low risk controls.
Brand 1977	Enrolled infants admitted to general and gastroenteritis wards.
Bruno 1996	Cohort study.
Burr 1993	Randomised mothers to give their infants soy formula if required or no soy formula.
Businco 1983	Cohort study.
Businco 1987	Cohort study.
Campbell 1989	Enrolled infants with infantile colic.
Carroccio 1997	Enrolled infants with CMA.
Carroccio 2000b	Enrolled infants with intolerance to hydrolysed proteins.
Carroccio 2000c	Enrolled infants with CMPI.
Chan 2002	Excess losses(28%). Trial of sole prolonged partially hydrolysed cow's milk formula versus cow's milk formula.
Chan-Yeung 2000	Had multiple allergy preventing co-interventions in treatment and not the control group.
Chandra 1986	Trial of maternal antigen avoidance during pregnancy and lactation.
Chandra 1989a	Original data unable to be verified.
Chandra 1989b	Original data unable to be verified.
Custovic 2000	Mite allergen avoidance trial, no hydrolysed formula group.
D'Agata 1996	Method of allocation unspecified. Substantial imbalances in numbers (50 fed partially hydrolysed whey formula, 15 cow's milk formula, 30 soy formula).
de Jong 1998	Trial of early supplementation of cow's milk formula versus a protein free placebo formula in breast fed infants.

(*Continued*)

Decsi 1998	Excess losses (27% hydrolysed formula group and 21% cow's milk formula group). Did not report clinical allergy. Reported growth.
Exl 1998	Allocated to intervention (breastfeeding, hydrolysed formula and delayed weaning) according to geographical area.
Fukushima 1997	Differential losses with excess losses in maternal and infant hydrolysed formula group (27%) and maternal hydrolysed formula and infant cow's milk formula group (23%). Trial of maternal allergen avoidance and infant supplemental or sole hydrolysed or cow's milk formula feeding where required.
Giampietro 2001	Enrolled infants with CMA.
Giovannini 1994	Excess post allocation losses (56 / 138) and not analysed in group of assignment (solely breast fed infants reported separately).
Gruskay 1982	Nonrandom allocation to soy or cow's mild formula.
Gustafsson 1992	Cohort study. No hydrolysed formula group.
Halken 1992	Excess losses after allocation (24%). Only infants who received hydrolysed formula included in analysis. Trial of prolonged supplementary or sole extensively versus partially hydrolysed, ultrafiltrated formula.
Hartman 1994	Abstract only. Losses unclear. Data not extractable from abstract.
Hattevig 1989	Trial of maternal allergen avoidance.
Hernell 2003	Method of allocation not reported. Allergy and growth rates not reported.
Hill 1995a	Enrolled infants with food reactions (to cow's molk, soy milk, casein and/or whey hydrolysate formula).
Hill 1995b	Enrolled infants with 'colic'.
Hill 1999	Enrolled infants with multiple food protein intolerance.
Hill 2000	Enrolled distressed infants with presumed gastroesophageal reflux.
Hill 2000b	Excess lost randomisation losses - 238/620 (38%).
Host 1988	Enrolled children with milk allergy.
Host 1991	Cohort study.
Iacono 1998	Enrolled infants (age 11 to 72 months) with chronic constipation.
Iikura 1995	Abstract form only. Method of allocation unclear, substantial differences in group sizes.
Isolauri 1995	Enrolled infants with CMA.

(*Continued*)

Keller 1996	Allocation performed by nurses 'at random'. "Maternal decision respected'. Unlikely to be random allocation.
Klemola 2002	Enrolled infants with CMA.
Lilja 1989	Trial of maternal allergen avoidance in pregnancy.
Lindfors 1988	Trial of early breastfeeding versus early adapted cow's milk formula.
Lothe 1982	Enrolled infants admitted with 'colic'.
Lucas 1984a	Preterm infants randomly allocated to feeds with banked breast milk or a preterm infant formula (either as sole or supplemental feeding). Hydrolysed formula not used.
Lucassen 2000	Enrolled infants with excessive crying.
Martinez-Valverde	No definition of allergic symptoms in 1st 4 months reported. In Spanish version of thesis, method of treatment allocation not extractable independently.
McLeish 1995	Enrolled infants with CMPI.
Medjad-Guillou 1992	Crossover trial.
Mihatsch 1999	Crossover trial examining effect of hydrolysed formula on plasma amino acids and gastrointestinal transit time.
Mihatsch 2002	Randomised trial of partially hydrolysed preterm infant formula versus adapted cow's milk formula in VLBW infants at low risk of atopy establishing enteral feeds. Excess post randomisation exclusions 48/135 (36%).
Miskelly 1988	Randomised infants to soy milk sole or supplementary feeding.
Mitchell 1977	Enrolled slightly undernourished Aboriginal children < 3years of age.
Moran 1992	Excessive losses (>20% in both groups). Trial of supplementary or sole hydrolysed formula versus cow's milk formula in low risk infants.
Nentwich 2003	Observational study.
Niggemann 2001	Enrolled infants with CMA / CMPI and atopic dermatitis.
Odelram 1996	Trial of extensively hydrolysed versus cow's milk formula for weaning of high risk infants. Excluded trial as 13 losses in addition to 9 post randomisation exclusions (total 27%).
Oggero 1994	Enrolled infants with colic and compared non-allergenic diet (soy or hydrolysed formula) with dicyclomine.
Palma 1996	Crossover study of subjects age 6 months to 99 years.
Paronen 2000	Enrolled infants at high genetic risk for diabetes. Did not measure allergy as outcome.

(*Continued*)

Pauls 1996	Enrolled preterm infants <1500g. Did not report allergy. Outcomes to day 6 reported only. Reported in abstract form only.
Polberger 1999	Preterm infants randomised to protein fortification with ultrafiltrated human milk or a bovine whey fortifier.
Raupp 1995	Excluded as excess post randomisation losses. Did not report allergy. Trial of sole hydrolysed formula versus cow's milk formula in low birth weight infants.
Riezzo 2001	Randomised trial of standard and hydrolysate formulas in preterm infants. Did not measure allergy or growth.
Rigo 1994a	Method of treatment allocation unclear. Allocated successive infants to formulas. Trial of 5 different types of hydrolysed formulas in healthy term infants. Extent of hydrolysis not reported. Allergy not reported. Only growth reported.
Rigo 1994b	Method of allocation not stated.
Sack 1994	Enrolled infants with acute diarrhoea.
Sampson 1991	Enrolled infants with CMA.
Savino 2003	Observational study enrolling infants with 'minor feeding problems'.
Schmelzle 2003	Randomised trial patially hydrolysed whey infant formula versus standard infant cow's milk formula. Excess losses - 52/154 (34%).
Schmidt 1995	Observational study (infants allocated formula at parents discretion).
Schmitz 1992	Exclude - did not report clinical allergy or growth. Excess losses at 1 year. Trial of early supplementry hydrolysed formula versus adapted cow's milk formula.
Schrander 1993	Cohort study of newborn infants to determine incidence of CMPI.
Seppo 2005	Enrolled infants with CMA.
Sicherer 2001	Enrolled infants with CMA.
Silva Rey 1996	Excess losses - 124 / 276 (45%) - 42 losses by 6 months and further 82 excluded post allocation. Method of allocation not reported.
Szajewska 2004	Randomised trial of extensively hydrolysed preterm formula versus partially hydrolysed preterm formula versus adapted cow's milk formula in high risk for atopy preterm infants. Excess post randomisation losses at all times - 22/90 (24%) at 4-5 months.
Tariq 1998	Cohort study.
Taubman 1988	Enrolled infants with excessive crying ('colic').

(*Continued*)

Terheggen-Lagro 2002	Enrolled infants with CMA.
Vaarala 1995	Growth and clinical allergy not reported.
Vandenplas 1988	Method of allocation not reported.
Vandenplas 1989	Retrospective study. Embedded intervention study, method of allocation not reported.
Zeiger 1989	Excluded as excess losses. Trial of maternal dietry avoidance in pregnancy and lactation, and infant allergen avoidance through encouragement of breast feeding with supplemental or weaning formula use and subsequent dietry restriction versus usual maternal diet and infant feeding with use of supplementary or weaning cow's milk formula.

DATA AND ANALYSES

Comparison 1. Early short term feeding: Hydrolysed formula vs human milk feeding - Low risk infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Childhood (incidence)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.38, 5.37]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Childhood (incidence)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 4.41]
2.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Eczema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Childhood (incidence)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 4.41]
3.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Childhood (incidence)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.38, 5.37]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Cow's milk allergy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	3559	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.46]
5.2 Childhood (incidence)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	7.11 [0.35, 143.84]
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Prolonged feeding: Hydrolysed formula vs human milk feeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. Early short term feeding: Hydrolysed formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Childhood (incidence)	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.33, 5.71]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

2.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Childhood (incidence)	1	77	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 73.26]
2.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Eczema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Childhood (incidence)	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.15]
3.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Childhood (incidence)	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.33, 5.71]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Cow's milk allergy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	3473	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 1.00]
5.2 Childhood (incidence)	1	77	Risk Ratio (M-H, Fixed, 95% CI)	5.13 [0.25, 103.43]
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 4. Prolonged feeding: Hydrolysed formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	7	2514	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.94]
1.2 Childhood (incidence)	2	950	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.05]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	4	318	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.04]
2.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.84]
2.3 Childhood (prevalence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.61]
3 Eczema	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	8	2558	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.68, 1.04]
3.2 Childhood (incidence)	2	950	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.63, 1.10]
3.3 Childhood (prevalence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.43, 1.02]
4 Rhinitis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	3	256	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.14, 1.85]
4.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.03]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.64, 5.16]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
6.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 5. Prolonged feeding: Hydrolysed formula vs cow's milk formula - Low risk infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight gain (g/kg/day)	3	82	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-3.20, -0.29]
1.1 Preterm formula	3	82	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-3.20, -0.29]
2 Head circumference change (cm/week)	1	21	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.16, 0.04]
2.1 Preterm formula	1	21	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.16, 0.04]
3 Length gain (cm/week)	1	21	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.27, 0.23]
3.1 Preterm formula	1	21	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.27, 0.23]

Comparison 6. Prolonged feeding: Hydrolysed formula vs cow's milk formula - High risk infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	7	2514	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.94]
1.2 Childhood (incidence)	2	950	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.05]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	4	318	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.04]
2.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.84]
2.3 Childhood (prevalence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.61]
3 Eczema	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	8	2558	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.68, 1.04]
3.2 Childhood (incidence)	2	950	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.63, 1.10]
3.3 Childhood (prevalence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.43, 1.02]
4 Rhinitis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	3	256	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.14, 1.85]
4.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.03]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.64, 5.16]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
6.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 7. Prolonged feeding: Extensively hydrolysed formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	2	1561	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.68, 1.13]
1.2 Childhood (incidence)	1	651	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.13]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.18, 2.04]
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	1	651	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.65, 1.59]
3 Eczema	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	3	1726	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.63, 1.08]
3.2 Childhood (incidence)	1	651	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.63, 1.17]
3.3 Childhood (prevalence)	1	651	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.02]
4 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	1	96	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.12, 66.22]
4.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	96	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.33, 4.02]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Weight gain (g/day)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-5.76, 1.72]
6.1 Preterm formula	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-5.76, 1.72]

Comparison 8. Prolonged feeding: Partially hydrolysed formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	7	1482	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.97]
1.2 Childhood (incidence)	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.10]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	4	268	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.28, 1.04]
2.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.84]
2.3 Childhood (prevalence)	1	432	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.70, 1.88]
3 Eczema	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	7	1361	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.69, 1.13]
3.2 Childhood (incidence)	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.61, 1.19]
3.3 Childhood (prevalence)	1	432	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.22]
4 Rhinitis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	3	206	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.70]
4.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.03]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [0.86, 7.56]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
6.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Weight gain (g/day)	2	46	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.90, 0.60]
7.1 Preterm formula	2	46	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.90, 0.60]

Comparison 9. Prolonged feeding: Extensively hydrolysed formula vs partially hydrolysed formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	3	1806	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.75, 1.16]
1.2 Childhood (incidence)	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.74, 1.18]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	2	341	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.74, 3.96]
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.35]
3 Eczema	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	4	1865	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.10]
3.2 Childhood (incidence)	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.67, 1.26]
3.3 Childhood (prevalence)	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.52]
4 Rhinitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	2	341	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.36, 4.29]
4.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	2	341	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.19, 0.99]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infancy (incidence)	1	246	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 1.16]
6.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Weight gain (g/day)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-4.57, 3.17]
7.1 Preterm formula	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-4.57, 3.17]

Comparison 10. Prolonged sole feeding: Hydrolysed formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	5	425	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.46, 0.80]
1.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.19, 0.90]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.25, 1.31]
2.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.84]
2.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Eczema	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	4	271	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.21]
3.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.14, 1.26]
3.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.03]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 11. Prolonged feeding: Hydrolysed formula vs cow's milk formula - Allergy / intolerance confirmed by test

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.22, 0.94]
1.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Atopic rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Atopic eczema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	1	35	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.64, 5.16]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

6.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
6.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Food intolerance	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.07, 3.33]
7.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 12. Prolonged feeding: Hydrolysed formula vs cow's milk formula - Blinded measurement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	3	2156	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.69, 1.08]
1.2 Childhood (incidence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.14]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.17, 1.42]
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.61]
3 Eczema	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	3	2124	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.14]
3.2 Childhood (incidence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.66, 1.18]
3.3 Childhood (prevalence)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.43, 1.02]
4 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.06, 35.37]
4.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.64, 5.16]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
6.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 13. Prolonged feeding: Hydrolysed formula vs cow's milk formula - Adequate methodology

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.85]
1.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

2 Asthma	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	2	174	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.23, 1.38]
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Eczema	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	2	174	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.68, 1.65]
3.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Rhinitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	2	174	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.70]
4.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.64, 5.16]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Weight gain (g/kg/day)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Preterm formula	2	66	Mean Difference (IV, Fixed, 95% CI)	-2.43 [-4.53, -0.34]

Comparison 14. Prolonged feeding: Partially hydrolysed whey formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Infancy (incidence)	6	1391	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.90]
1.2 Childhood (incidence)	2	510	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.31, 1.52]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Asthma	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	3	177	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.29, 1.28]
2.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.84]
2.3 Childhood (prevalence)	1	432	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.70, 1.88]
3 Eczema	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	6	1270	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.65, 1.09]
3.2 Childhood (incidence)	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.61, 1.19]
3.3 Childhood (prevalence)	1	432	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.22]
4 Rhinitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.70]
4.2 Childhood (incidence)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.03]
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Cow's milk allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.89]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Weight gain (g/day)	2	46	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.90, 0.60]
6.1 Preterm formula	2	46	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.90, 0.60]

Comparison 15. Prolonged feeding: Partially hydrolysed casein containing formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.80, 2.31]
1.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.60]
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Eczema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.66, 2.55]
3.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [0.86, 7.56]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Weight gain (g/day)	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.32 [-4.83, 2.19]
6.1 Preterm formula	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.32 [-4.83, 2.19]

Comparison 16. Prolonged feeding: Extensively hydrolysed whey formula vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	1	972	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.34]
1.2 Childhood (incidence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.38]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.73, 1.94]
3 Eczema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	1	972	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.72, 1.40]
3.2 Childhood (incidence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.49]
3.3 Childhood (prevalence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.46, 1.33]

Comparison 17. Prolonged feeding: Extensively hydrolysed casein formula containing vs cow's milk formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any allergy	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Infancy (incidence)	2	1072	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]
1.2 Childhood (incidence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.53, 0.97]
1.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Asthma	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Infancy (incidence)	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.18, 2.04]
2.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Childhood (prevalence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.49, 1.45]
3 Eczema	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Infancy (incidence)	3	1237	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.51, 0.97]
3.2 Childhood (incidence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.44, 0.98]
3.3 Childhood (prevalence)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.27, 0.92]
4 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Infancy (incidence)	1	96	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.12, 66.22]
4.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Food allergy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Infancy (incidence)	1	96	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.33, 4.02]
5.2 Childhood (incidence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Childhood (prevalence)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Weight gain (g/day)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-5.76, 1.72]
6.1 Preterm formula	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-5.76, 1.72]

WHAT'S NEW

Last assessed as up-to-date: 26 July 2006.

18 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 4, 2003

27 July 2006	New search has been performed	Eligibility of all trials was reviewed. Several new studies and updated reports were included. Comparisons were partially redone to better meet the objectives and methodology specified in the protocol. Additional, previously specified subgroup analyses were performed according to studies which had blinded measurement for allergy, enrolled infants that were solely formula fed, and were fed 100% whey formula or casein containing formula (according to degree of hydrolysis) . The exclusion of 2 previously included trials and inclusion of a new large trial result in substantial changes to the review and conclusions.
27 July 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Both reviewers independently performed literature search, extracted data and checked accuracy of review. Both reviewers independently performed literature search, extracted data and checked accuracy of the updated review.

DECLARATIONS OF INTEREST

Both authors have been invited speakers at industry organised scientific meetings. Neither has accepted an honorarium.

SOURCES OF SUPPORT

Internal sources

- RPA Newborn Care, Royal Prince Alfred Hospital, Australia.

External sources

- Centre for Perinatal Health Services Research, University of Sydney, Australia.

NOTES

This is a substantive update of the previously withdrawn version of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Proteins; Food Hypersensitivity [*prevention & control]; Hydrolysis; Infant, Newborn; Infant Formula [*chemistry]; Milk, Human; Milk Hypersensitivity [prevention & control]; Protein Hydrolysates [administration & dosage]; Randomized Controlled Trials as Topic; Synapsins

MeSH check words

Humans; Infant