**APPENDIX**

**Table 1. Characteristics of included reviews**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Alexander**  **& Cabana (2010)** | **Osborn & Sinn (Cochrane review 2006)** | **Szajewska**  **& Horvath (2010)** |
| **Searching** | April 2009 | 2006 | Sept 2009 |
| **CENTRAL** |  | + | + |
| **MEDLINE** | + | + | + |
| **EMBASE** | + | + | + |
| **CINAHL** |  | + | + |
| **Others** | Bibliographies of reviews and articles | Previous reviews including cross- references. | Reference lists |
| **Unpublished data** | No | Yes | Yes |
| **Language restriction** |  | Mainly in English | No |
| **Population** | Healthy infants at high risk of developing allergy° (except 1 study in unselected general population) | Infants <6 mo without clinical evidence of allergy | Healthy term infants at high risk of developing allergy° and/or other markers |
| **Intervention** | whey pHF | Early short-term (average four days) or prolonged (4 to 6 months) use of an HF (any type) | whey pHF |
| **Comparison** | CMF | Human milk or cow milk | CMF, eHF |
| **Outcome (primary)** | Atopic dermatitis (infant eczema) or an outcome that included atopic dermatitis (e.g., variable labeled ‘skin symptoms’ that included AD) | All allergic disease and food intolerance | (1) all allergic diseases including atopic eczema/atopic dermatitis,  gastrointestinal symptoms, food allergy/hypersensitivity,  respiratory symptoms (wheezing and/or asthma),  allergic rhinitis, and urticaria (if reported together), and  (2) atopic eczema/atopic dermatitis. |
| **Outcome (secondary)** | N/A | Asthma, atopic dermatitis/eczema, allergic rhinitis, cow milk or soy protein allergy or intolerance, food allergy or intolerance, urticaria and anaphylaxis | Respiratory symptoms (wheezing, asthma), allergic rhinitis, food allergy/hypersensitivity, urticaria, and anaphylaxis. |
| **Study designs** | Clinical and observational epidemiologic peer-reviewed studies | RCT & quasi-RCT  with >80% follow up | RCT & quasi-RCT |
| **Assessment of study quality** | + | + | + |
| **Methods of synthesis** | Summary relative risk estimates (SRRE), 95% CI | RR (FE), 95% CI | RR (FE & RE)  NNT, 95% CI |
| **Number of studies/number of patients** | 18 publications (12 study populations) | 18 (7680) | 15 publications (12 study populations) (3284 participants (1027 in the pHF groups and 2257 in the control groups) |

**Legend:** Healthy infants at high risk of developing allergy°: allergy in at least one parent and/or sibling

**Table 2. Methodological quality of included reviews (based on AMSTAR assessments)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Alexander**  **& Cabana (2010)** | **Osborn & Sinn (Cochrane review 2006)** | **Szajewska**  **& Horvath (2010)** |
| 1. | Was an ‘a priori’ design provided? | Yes | Yes | Yes |
| 2. | Was there duplicate study selection and data extraction? | Can’t answer | Yes | Yes |
| 3. | Was a comprehensive literature search performed? | Yes | Yes | Yes |
| 4. | Was the status of publication (i.e. grey literature) used as an inclusion criterion? | No | Yes | Yes |
| 5. | Was the list of studies (included and excluded) provided? | Yes | Yes | Yes |
| 6. | Were the characteristics of the included studies provided? | Yes | Yes | Yes |
| 7. | Was the scientific quality of the included studies assessed and documented? | Yes | Yes | Yes |
| 8. | Was the scientific quality of the included studies used appropriately in formulating conclusions? | Yes | Yes | Yes |
| 9. | Were the methods used to combine the findings of studies appropriate? | Yes | Yes | Yes |
| 10. | Was the likelihood of publication bias assessed? | Yes | No | No |
| 11. | Was the conflict of interest stated? | Yes | Yes | Yes |

**Table 3. Any hydrolyzed formula *versus* standard cow milk formula (intervention during 4 to 6 months)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ref. | **Outcome** | **Age at follow-up** | **RCTs (n)** | **Effect size** |
|  | ***High risk infants*** |  |  |  |
| CR | **Any allergy** | **Infancy (incidence)** | **7 (2514)** | **0.79 (0.66 to 0.94)** |
| CR | Any allergy | Childhood (incidence) | 2 (950) | 0.85 (0.69 to 1.05) |
| CR | Asthma | Infancy (incidence) | 4 (318) | 0.57 (0.31 to 1.04) |
| CR | Asthma | Childhood (incidence) | 1 (78) | 0.38 (0.08 to 1.84) |
| CR | Asthma | Childhood (prevalence) | 1 (872) | 1.06 (0.70 to 1.61) |
| CR | Eczema | Infancy (incidence) | 8 (2558) | 0.84 (0.68 to 1.04) |
| CR | Eczema | Childhood (incidence) | 2 (950) | 0.83 (0.63 to 1.10) |
| CR | Eczema | Childhood (prevalence) | 1 (872) | 0.66 (0.43 to 1.02) |
| CR | Rhinitis | Infancy (incidence) | 3 (256) | 0.52 (0.14 to 1.85) |
| CR | Rhinitis | Childhood (incidence) | 1 (78) | 0.48 (0.04 to 5.03) |
| CR | Food allergy | Infancy (incidence) | 1 (141) | 1. 82 (0.64 to 5.16) |
| CR | **Cow milk allergy** | **Infancy (incidence)** | **1 (67)** | **0.36 (0.15 to 0.89)** |

**Table 4. Partially hydrolyzed formula *versus* standard cow milk formula**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Outcome** | **Age at follow-up** | **RCTs (n)** | **Effect size** |
|  | **ANY partially hydrolyzed formula** | | | |
| CR | **Any allergy** | **Infancy (incidence)** | **7 (1482)** | **0.79 (0.65 to 0.97)** |
| CR | Any allergy | Childhood (incidence) | 2 (510) | 0.86 (0.67 to 1.10) |
| CR | Asthma | Infancy (incidence) | 4 (268) | 0.54 (0.28 to 1.04) |
| CR | Asthma | Childhood (incidence) | 1 (78) | 0.38 (0.08 to 1.84) |
| CR | Asthma | Childhood (prevalence) | 1 (432) | 1.15 (0.70 to 1.88) |
| CR | Eczema | Infancy (incidence) | 7 (1361) | 0.89 (0.69 to 1.13) |
| CR | Eczema | Childhood (incidence) | 2 (510) | 0.85 (0.61 to 1.19) |
| CR | Eczema | Childhood (prevalence) | 1 (432) | 0.71 (0.41 to 1.22) |
| CR | Rhinitis | Infancy (incidence) | 3 (206) | 0.40 (0.09 to 1.70) |
| CR | Rhinitis | Childhood (incidence) | 1 (78) | 0.48 (0.04 to 5.03) |
| CR | Food allergy | Infancy (incidence) | 1 (91) | 2. 56 (0.86 to 7.56) |
| CR | Cow milk allergy | Infancy (incidence) | 1 (67) | 0.36 (0.15 to 0.89) |
|  | **Partially hydrolyzed WHEY formula** | | | |
| CR | **Any allergy** | **Infancy (incidence)** | **6 (1391)** | **0.73 (0.59 to 0.90)** |
| CR | Any allergy | Childhood (incidence) | 2 (510) | 0.68 (0.31 to 1.52) |
| CR | Asthma | Infancy (incidence) | 3 (177) | 0.61 (0.29 to 1.28) |
| CR | Asthma | Childhood (incidence) | 1 (78) | 0.38 (0.08 to 1.84) |
| CR | Asthma | Childhood (prevalence) | 1 (432) | 1.15 (0.70 to 1.88) |
| CR | Eczema | Infancy (incidence) | 6 (1270) | 0.84 (0.65 to 1.09) |
| CR | Eczema | Childhood (incidence) | 2 (510) | 0.85 (0.61 to 1.19) |
| CR | Eczema | Childhood (prevalence) | 1 (432) | 0.71 (0.41 to 1.22) |
| CR | Rhinitis | Infancy (incidence) | 2 (115) | 0.40 (0.09 to 1.70) |
| CR | Rhinitis | Childhood (incidence) | 1 (78) | 0.48 (0.04 to 5.03) |
| CR | **Cow milk allergy** | **Infancy (incidence)** | **1 (67)** | **0.36 (0.15 to 0.89)** |
| S&H | All allergic diseases (incidence) | 3-6 mo | 5 (169/204) | 0.48 (0.23 to 1.00) |
|  | **12 mo** | **4 (371/399)** | **0.62 (0.45 to 0.85)** |
|  | 24 mo | 2 (65/79) | 0.63 (0.37 to 1.09) |
|  | **30-36 mo** | **2 (40/38)** | **0.42 (0.19 to 0.90)** |
| S&H | All allergic diseases (cumulative incidence) | **0-6 mo** | **2 (28/30)** | **0.16 (0.04 to 0.67)** |
|  | 0-12 mo | 2 (585/586) | 0.62 (0.33 to 1.18) |
|  | **0-36 mo** | **3 (638/643)** | **0.71 (0.6 to 0.85)** |
|  | 0 to 5-6 y | 2 (585/586) | 0.69 (0.42 to 1.14) |
| S&H | Eczema (incidence) | 4-6 mo | 5 (167/194) | 0.58 (0.27 to 1.22) |
|  | **12 mo** | **4 (352/372)** | **0.68 (0.48 to 0.98)** |
|  | 24 mo | 3 (118/136) | 0.82 (0.4 to 1.67) |
|  | 30-36 mo | 2 (93/95) | 1.3 (0.07 to 22.7) |
| S&H | Eczema (cumulative incidence) | **0-3 mo** | **1 (53/57)** | **0.25 (0.07 to 0.82)** |
|  | **0-6 mo** | **2 (85/92)** | **0.3 (0.14 to 0.66)** |
|  | 0-12 mo | 3 (638/643) | 0.58 (0.32 to 1.04) |
|  | **0-18 mo** | **1 (53/57)** | **0.34 (0.16 to 0.73)** |
|  | **0-24 mo** | **1 (53/57)** | **0.52 (0.29 to 0.92)** |
|  | **0-36 mo** | **3 (638/643)** | **0.71 (0.58 to 0.88)** |
|  | **0 to 5-6 y** | **2 (585/586)** | **0.8 (0.67 to 0.97)** |
| A&C | Atopic dermatitis | **All studies** | **11 (N/A)** | **0.55 (0.4 to 0.76)\*** |
|  | **6 mo** | **4 (N/A)** | **0.41 (0.31 to 0.54)** |
|  | **12 mo** | **7 (N/A)** | **0.59 (0.41 to 0.87)** |
|  | >12 mo | 6 (N/A) | 0.76 (0.57 to 1.00) |
| A&C | Atopic dermatitis (top-tier studies) | **All studies** | **4 (N/A)** | **0.45 (0.3 to 0.7)\*** |
|  | **≤12 mo** | **4 (N/A)** | **0.45 (0.3 to 0.7)** |
|  | **≥30 mo** | **4 (N/A)** | **0.64 (0.47 to 0.88)** |
|  | **Partially hydrolyzed CASEIN formula** | | | |
| CR | Any allergy | Infancy (incidence) | 1 (91) | 1.36 (0.80 to 2.31) |
|  | Asthma | Infancy (incidence) | 1 (91) | 0.34 (0.07 to 1.60) |
|  | Eczema | Infancy (incidence) | 1 (91) | 1.30 (0.66 to 2.55) |
|  | Food allergy | Infancy (incidence) | 1 (91) | 2.56 (0.86 to 7.56) |

\*SRRE, summary relative risk estimate

N/A, not available

**Table 5. Extensively hydrolyzed formula *versus* standard cow milk formula (intervention during 4-6 months)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Outcome** | **Age at follow-up** | **RCTs (n)** | **Effect size** |
| CR | Any allergy | Infancy (incidence) | 2 (1561) | 0.87 (0.68 to 1.13) |
| CR | Any allergy | Childhood (incidence) | 1 (651) | 0.89 (0.71 to 1.13) |
| CR | Asthma | Infancy (incidence) | 1 (96) | 0.61 (0.18 to 2.04) |
| CR | Asthma | Childhood (prevalence) | 1 (651) | 1.02 (0.63 to 1.59) |
| CR | Eczema | Infancy (incidence) | 3 (1726) | 0.83 (0.58 to 1.21) |
| CR | Eczema | Childhood (incidence) | 1 (651) | 0.86 (0.63 to 1.17) |
| CR | Eczema | Childhood (prevalence) | 1 (651) | 0.64 (0.40 to 1.02) |
| CR | Rhinitis | Infancy (incidence) | 1 (96) | 2.76 (0.12 to 66.22) |
| CR | Food allergy | Infancy (incidence) | 1 (96) | 1.15 (0.33 to 4.02) |
|  | **Extensively hydrolyzed WHEY formula** | | | |
| CR | Any allergy | Infancy (incidence) | 1 (972) | 0.97 (0.71 to 1.34) |
| CR | Any allergy | Childhood (incidence) | 1 (431) | 1.07 (0.82 to 1.38) |
| CR | Asthma | Childhood (prevalence) | 1 (431) | 1.19 (0.73 to 1.94) |
| CR | Eczema | Infancy (incidence) | 1 (972) | 1.00 (0.72 to 1.40) |
| CR | Eczema | Childhood (incidence) | 1 (431) | 1.06 (0.75 to 1.49) |
| CR | Eczema | Childhood (prevalence) | 1 (431) | 0.78 (0.46 to 1.33) |
|  | **Extensively hydrolyzed CASEIN formula** | | | |
| CR | Any allergy | Infancy (incidence) | 2 (1072) | 0.79 (0.58 to 1.06) |
| CR | **Any allergy** | **Childhood (incidence)** | **1 (431)** | **0.72 (0.53 to 0.97)** |
| CR | Asthma | Infancy (incidence) | 1 (96) | 0.61 (0.18 to 2.04) |
| CR | Asthma | Childhood (prevalence) | 1 (431) | 0.84 (0.49 to 1.45) |
| CR | **Eczema** | **Infancy (incidence)** | **3 (1237)** | **0.71 (0.51 to 0.97)** |
| CR | **Eczema** | **Childhood (incidence)** | **1 (431)** | **0.66 (0.44 to 0.98)** |
| CR | **Eczema** | **Childhood (prevalence)** | **1 (431)** | **0.50 (0.27 to 0.92)** |
| CR | Rhinitis | Infancy (incidence) | 1 (96) | 2.76 (0.12 to 66.22) |
| CR | Food allergy | Infancy (incidence) | 1 (96) | 1.15 (0.33 to 4.02) |

**Table 6. Extensively hydrolyzed formula versus partially hydrolyzed formula (intervention during 4 to 6 months)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Outcome** | **Age at follow-up** | **RCTs (n)** | **Effect size** |
| CR | Any allergy | Infancy (incidence) | 3 (1806) | 0.93 (0.75 to 1.16) |
| CR | Any allergy | Childhood (incidence) | 1 (661) | 0.93 (0.74 to 1.18) |
| CR | Asthma | Infancy (incidence) | 2 (341) | 1.72 (0.74 to 3.96) |
| CR | Asthma | Childhood (prevalence) | 1 (661) | 0.89 (0.58 to 1.35) |
| CR | Eczema | Infancy (incidence) | 4 (1865) | 0.89 (0.73 to 1.10) |
| CR | Eczema | Childhood (incidence) | 1 (661) | 0.92 (0.67 to 1.26) |
| CR | Eczema | Childhood (prevalence) | 1 (661) | 0.90 (0.54 to 1.52) |
| CR | Rhinitis | Infancy (incidence) | 2 (341) | 1.25 (0.36 to 4.29) |
| CR | **Food allergy** | **Infancy (incidence)** | **2 (341)** | **0.43 (0.19 to 0.99)** |
| CR | Cow milk allergy | Infancy (incidence) | 1 (246) | 0.13 (0.01 to 1.16) |

## Search methods for identification of reviews

## The *Cochrane Database of Systematic Reviews* and the *Database of Abstracts of Reviews of Effects* (DARE) were searched for all systematic reviews that focused on hydrolyzed formulas for preventing atopy and allergy. The terms such as ‘infant nutrition’ OR ‘formula’ AND (‘hypersensitivity’ OR ‘allergy’ OR ‘asthma’ OR ‘eczema’ OR ‘rhinitis’ OR ‘food intolerance’) AND (‘prevention’ OR ‘prophylaxis’) were entered in the search field for the review title, abstract, or keywords. Experts in the field were contacted for additional references. The latest search was conducted in October 2011, and the search was updated in January 2013. There was no language of publication restriction imposed.

### Assessment of methodological quality of included reviews

### The AMSTAR tool was used, which is a measurement tool created to assess the methodological quality of systematic reviews. The AMSTAR tool includes the following criteria: establishing the research question and inclusion criteria before the conduct of the review, data extraction by at least two independent data extractors, comprehensive literature review with searching of at least two databases, key word identification, expert consultation and limits applied, detailed list of included/excluded studies and study characteristics, quality assessment of included studies and consideration of quality assessments in analysis and conclusions, appropriate assessment of homogeneity, assessment of publication bias, and a statement of any conflict of interest.

# *Systematic review of subsequently published trials*

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis and the PRISMA statement were followed.

# Criteria for considering studies for this review

**Types of studies, participants, interventions, and outcomes**

The same criteria as described in the *Methods* for overview of reviews were applied, but primary RCTs and quasi-RCTs were included rather than reviews.

## Search methods

## Searches were performed of the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, EMBASE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases starting from the date of the most recent search in the included reviews. The search terms relevant to hydrolyzed formula were used. No language restrictions were applied.

**Searching other resources**

In addition, we searched 2 trial registries (ClinicalTrials.gov, www.clinicaltrials.gov, and EU Clinical Trials Register, www.clinicaltrialsregister.eu) and proceedings from major scientific gastrointestinal meetings such as ESPGHAN, NASPGHAN, and EAACI published in the last 3 years. No attempt was made to identify unpublished data.

## Data collection and analysis

First, the title, abstract, and keywords of every record identified with the search strategy were screened. The full text of potentially relevant trials and of records for which the relevance was unclear was retrieved. The reviewer applied the inclusion criteria to each potentially relevant trial to determine its eligibility.

**Data extraction and management**

Data extraction was performed using standard data-extraction forms. For dichotomous outcomes, the total number of participants and the number of participants who experienced the event were extracted. For continuous outcomes, the total number of participants and the means and standard deviations were extracted. If feasible, the data were entered into Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, for analysis.

### Assessment of risk of bias in included studies

The Cochrane Collaboration’s tool for assessing risk of bias was used, which includes the following criteria: adequacy of sequence generation, allocation concealment, and blinding of participants, personnel and outcome assessors; incomplete outcome data are addressed, free of selective outcome reporting, and free of other sources of bias. In all cases, an answer of ‘*yes*’ indicates a low risk of bias, and an answer of ‘*no*’ indicates a high risk of bias.

**Alexander & Cabana (2010)**

The authors’ objective was to validate the efficacy of using a whey protein partially hydrolyzed formula compared with cow milk formula in reducing the risk of atopic dermatitis. MEDLINE and EMBASE were searched up until April 2009; the search terms were reported. In addition, published reviews and reference lists of included studies were screened. Clinical and observational epidemiologic studies that compared healthy infants at high risk for developing allergy (except one population based study in unselected infants) who received **partially hydrolyzed whey protein** **formula** with infants who received cow milk formula and assessed the risk of atopic dermatitis (infant eczema) and reported an outcome that included the risk or incidence of atopic dermatitis were eligible for inclusion. The authors did not state how the papers were selected for the review or how many reviewers performed the selection (presumably both reviewers). The reviewers assessed the methodological quality of the studies, evaluating the following criteria: the definition of high-risk status for allergy, loss to follow-up after randomization, duration of dietary intervention, scope and compliance with dietary restrictions, trial blinding procedures among study participants and researchers, clinical and diagnostic procedures, overall and within-groups sample sizes, data analysis technique, and control of potential bias and confounding factors. Random effects models were used to calculate summary relative risk estimates (SRRE), with 95% CI and corresponding P values for heterogeneity. Publication bias was assessed by generating funnel plots for a visual examination, conducting correlation and regression tests for significance, and using a ‘trim-and-fill’ procedure to evaluate symmetry around the summary effect.

Eighteen articles representing 12 independent study populations met the inclusion criteria. Among them, 6 studies representing 4 infant populations were considered methodologically superior. For atopic dermatitis, meta-analysis of all reviewed studies that specifically reported data for atopic dermatitis and studies that reported outcomes that included atopic dermatitis (e.g., atopy, skin symptoms) showed that feeding with **partially hydrolyzed whey protein** **formula** statistically significantly reduced the risk of atopic manifestations (11 trials, SRRE 0.56, 95% CI 0.4 to 0.77). Meta-analysis of studies of higher methodological quality also documented significant risk reduction (4 trials; SRRE 0.45, 95% CI 0.30 to 0.70). The effect was consistent, regardless of study design, infant population, follow-up time, or study location. The authors concluded that feeding with partially hydrolyzed whey protein formula instead of cow milk formula reduced the risk atopic dermatitis in infants with a family history of allergy.

**Osborn & Sinn (Cochrane review 2006)**

The authors’ main objective was to assess the effect of feeding hydrolyzed formulas compared to adapted cow milk or human breast milk on allergy and food intolerance in infants and children. If hydrolyzed formulas were effective, another objective was to determine what type of hydrolyzed formula is most effective (i.e., extensively versus partially hydrolyzed formulas). The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and CINAHL were searched up until March 2006; the search terms were reported. In addition, previous reviews were examined and reference lists of included trials were screened. The search was mainly for articles in the English language. Randomized and quasi-randomized trials, with >80% follow up of participants, were eligible for inclusion if they compared the use of a hydrolyzed infant formula to human milk or cow milk formula. The primary outcomes were all allergy (including asthma, atopic dermatitis, allergic rhinitis or food allergy) and food intolerance. Secondary outcomes included asthma, atopic dermatitis/eczema, allergic rhinitis, cow milk or soy protein intolerance, cow milk or soy protein allergy, food allergy, food intolerance, urticaria, and anaphylaxis. In addition, potential harms such as growth parameters, cost, and infant feed refusal were assessed. Two reviewers independently screened articles for inclusion. Any differences were resolved by consensus. Two reviewers independently assessed validity using the following criteria: adequacy of randomization and allocation concealment, blinding of parents or care providers and assessors to intervention, and completeness of assessment in all randomized individuals. Pooled risk ratios with 95% CI were calculated for dichotomous data using a fixed effects model. Eighteen RCTs involving 7680 participants were included.

**Szajewska & Horvath (2010)**

The authors' objective was to evaluate data on the efficacy of using a **partially hydrolyzed whey formula** to reduce the risk of allergy in healthy infants at high risk of allergy. The Cochrane Library, MEDLINE, EMBASE, and CINAHL were searched for articles from inception until September 2009. The search terms were reported. In addition, reference lists from retrieved articles and published key reviews were screened. The manufacturer of a partially hydrolyzed whey formula was contacted for unpublished data. Published letters to the editor, abstracts, and proceedings from scientific meetings were only included if a full set of data could be obtained from their authors. No language restrictions were applied. Randomized controlled trials (RCTs) and quasi‐RCTs were eligible for inclusion if they compared use of a partially hydrolyzed whey formula with a standard infant formula or an extensively hydrolyzed formula, containing hydrolyzed bovine proteins (whey or casein), for prevention of allergies in healthy full‐term infants who were at high risk of developing an allergy. The risk of developing an allergy was assessed by the family history and other described markers. The primary outcomes were all allergic diseases and atopic eczema/atopic dermatitis. The secondary outcomes were respiratory symptoms, allergic rhinitis, food allergy or hypersensitivity, urticaria, and anaphylaxis. Included trials were conducted in industrialized countries and, where reported, interventions lasted from 3 to 12 months. Definitions of atopic eczema or atopic dermatitis varied between trials. Some trials assessed formula in addition to breastfeeding, and one assessed formula in addition to weaning food after a certain time period. Some trials included co‐interventions, such as dietary restrictions, or the avoidance of tobacco smoke, pets, and damp housing conditions. Two reviewers independently screened articles for inclusion and discrepancies were resolved by consensus. Two reviewers independently assessed the quality of the included trials, using the Cochrane Collaboration's tool for assessing risk of bias, which includes criteria for the adequacy of sequence generation, allocation concealment, blinding, completeness of follow‐up data, and bias from selective outcome reporting and other sources. Each criterion required a ‘yes’ (indicating a low risk of bias) or ‘no’ (indicating a high risk of bias) response. The number of participants who experienced each outcome was extracted to calculate risk ratios and their 95% confidence intervals. Trial authors were contacted for further data, when necessary. The data were extracted by one reviewer and checked by a second, with discrepancies resolved through consensus. Fixed‐effect and random‐effects models were used to pool the risk ratios and their 95% confidence intervals. The numbers needed to treat were also calculated. Heterogeneity was assessed using the X2 and I2 statistics. While the authors intended to assess publication bias using a funnel plot, this was not performed due to the small number of studies (<10) included in the analyses of primary outcomes measures. A number of subgroup analyses were undertaken on the incidence and cumulative incidence of allergic diseases and eczema, in several age groups and by per protocol or intention‐to‐treat analysis. Sensitivity analyses were conducted to remove trials with low methodological quality, which were those with unclear or inadequate methods of randomization or allocation concealment.

**Lowe AJ et al. (2011)**

We identified one eligible study (19) that was published subsequent to the latest meta-analyses. This was a single-blind RCT designed to assess the effect of using a pHF-W at weaning on the risk of allergic disease. This trial from Australia recruited infants with a positive family history of allergic disease (Melbourne Atopy Cohort Study, MACS) (n=620). The trial had 3 arms and participants were randomized to receive at partial or full cessation of breastfeeding one of 3 infant formulas: cow milk formula (CMF, n=206), soy formula (n=208), or pHF-W (n=206). Study formulas were offered until the end of the first year of life. The methods of randomization were unclear. The first 97 infants were randomized to 2 arms only (CMF or soy formula); afterwards, when pHF became available, a new randomization list was generated with a higher proportion of infants allocated to the pHF group to obtain equal numbers in each formula group. Insufficient information was provided to allow judgment of allocation concealment. The study was conducted single-blind (participant). Intention-to-treat analysis was performed. The primary outcome measure was the development of any allergic manifestations (eczema, food reaction, any allergic manifestation, positive skin prick test) assessed during 18 telephone interviews with parents. The investigators reported that at 2 years, 575 (93%) infants out of 620 were followed-up, and at 6 to 7 years, 495 (80%). Feeding with pHF compared with CMF did not significantly affect the risk of developing any allergic disease at 0-1 y (OR 1.02, 95% CI 0.67 to 1.54) or at 0-2 y (OR 1.21, 95% CI 0.81 to 1.8). There was also no difference between the group fed pHF and the group fed CMF for any of the secondary outcomes within the first 2 y and at 6-7 y. The authors concluded that there was no evidence that introducing pHF at the cessation of breastfeeding reduced the risk of allergic manifestations, including eczema, asthma, and allergic rhinitis. There were some methodological issues with the trial that call for caution when interpreting the results (20).These include the unclear reason for publishing the results 15 years after collecting the data, outcome assessment through telephone interviews with parents, and changing definitions of outcome parameters compared to previous publications on this cohort