Hydrolysed formula and Risk of Allergic or Autoimmune Outcomes: a systematic review and meta-analysis (Review C Part I).

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1. Background and Methodology

Review C Part I is one of 4 reports resulting from a comprehensive review of the scientific literature on infant feeding and the development of atopic and autoimmune diseases, commissioned by the UK Food Standards Agency. Atopic conditions such as asthma, eczema, rhinoconjunctivitis and food allergy appear to have increased in prevalence in recent decades in many countries, and are some of the commonest causes of chronic illness in children and young adults living in the UK (1, 2)(3)(4)(5). An apparent increase in disease prevalence, combined with data from migration studies, suggests that early-life environmental factors may be important modulators of atopic disease risk. Similarly the autoimmune diseases type I diabetes mellitus and Crohn's disease appear to have increased in some countries (6). Significant attention has focussed on early-life dietary exposures in relation to these atopic and autoimmune diseases, due to recent changes in the human diet, and the potential effects of such changes on intestinal and systemic immune development (7). The gut associated lymphoid tissue is our largest collection of immune tissue, and our most mature immune organ at the time of birth (8). So enteral exposures in infancy are likely to be especially potent modulators of immune development and risk of immune-mediated disease. Although there are a large number of observational studies, some intervention trials and several systematic reviews in this area, they tend to focus on one specific area of diet and a limited number of immune outcomes. The purpose of this project is to assess comprehensively and systematically the existing literature regarding the relationship between dietary exposures during pregnancy, lactation and infancy, and a child's risk of developing any of the common atopic and autoimmune diseases.

This project consists of a series of systematic reviews which together have very broad inclusion criteria and were registered as 3 separate review protocols on the International Prospective Register of Systematic Reviews (PROSPERO references CRD42013003802 – REVIEW A; CRD42013004239 – REVIEW B; CRD42013004252 – REVIEW C; www.crd.york.ac.uk/Prospero) on the 5th August 2013. The overall purpose of the work is to inform UK Government feeding guidance for mothers and their infants.

The outcomes of this project will be summarised in 4 separate reports, with a distinct set of dietary exposures examined in each report:

1. REVIEW A: DURATION OF TOTAL AND EXCLUSIVE BREASTFEEDING, AND TIMING OF SOLID FOOD INTRODUCTION
2. REVIEW B: TIMING OF INTRODUCTION OF ALLERGENIC FOODS INTO THE INFANT DIET
3. REVIEW C PART I: HYDROLYSED FORMULA IN PLACE OF STANDARD UNHYDROLYSED COW'S MILK BASED INFANT FORMULA, OR BREAST MILK
4. REVIEW C PART II: OTHER MATERNAL AND INFANT DIETARY EXPOSURES

The specific outcomes of interest for all of these reviews, chosen due to their high prevalence in the UK population, and described in more detail below, are:

Atopic disorders: Food allergy, Eczema, Asthma, Allergic rhinitis, Allergic conjunctivitis, Allergic sensitisation

Autoimmune disorders: Type 1 diabetes mellitus, Coeliac disease, Inflammatory bowel disease, Autoimmune thyroid disease, Juvenile rheumatoid arthritis, Vitiligo, Psoriasis.

1.1. Review C Part I: Hydrolysed formula in place of standard unhydrolysed cow's milk based infant formula, or breast milk

Attention has focussed on the role of infant enteral exposure to intact cow's milk protein due to early observations showing an association between use of infant formula and eczema (9), and to more recent clinical and immunological studies suggesting a link between infant formula and risk of insulin dependent diabetes, perhaps due to immunological cross reactivity between bovine insulin present in milk formula, and human insulin (10). Cow's milk formula contains proteins from 14 kilo Daltons (kD; α-lactalbumin) in size, up to 67 kD (bovine serum albumin). Allergenic peptides are usually 10 to 70 kD in size, with many in the 10 to 40 kD range. There is no universally accepted definition of a pHF or eHF. eHF is intended to have no peptides of ≥3 kD, and pHF no peptides >5 kD. Independent studies have found that pHF pHF contains 15-20% peptides over the target size, and eHF up to 5%, and both pHF and eHF are capable of eliciting immunological and clinical allergic reactions in some cow's milk allergic people (11). For the purposes of this systematic review, we have not used a specific definition of hydrolysed formula, but definitions (if any) and trade names used in individual studies were noted and used to interpret the findings of the review, by inclusion in the Characteristics of Included Studies Table.

1.2. Specific questions addressed in Review C Part I

This review addressed 3 key research questions, to help understand the potential role of hydrolysed cow's milk formula for reducing an infant's risk of atopic or autoimmune disease:

a) Does the use of either extensively or partially hydrolysed cow's milk formula feeding, in place of either standard cow's milk formula or breast milk, influence children's future risk of developing atopic or autoimmune disease?

b) Does the extent of protein hydrolysis (ie partial versus extensive hydrolysis) in a hydrolysed cow's milk formula influence children's future risk of developing atopic or autoimmune disease?

c) Does the fraction of cow's milk (whey versus casein) used to make a hydrolysed cow's milk formula influence children's future risk of developing atopic or autoimmune disease?

1.3. Glossary of key terms

Allergic sensitisation: production of specific IgE antibodies directed against harmless environmental antigens such as pollens, mites, milk, egg or peanut; or production of increased serum total IgE levels. Allergic sensitisation is strongly associated with Atopic disease.

Atopic disease: chronic health conditions associated with (but not always directly caused by) the production of IgE antibodies to harmless environmental antigens.

CCT: Controlled clinical trial. An intervention trial which used a predicatable allocation sequence, thought likely to lead to unbalanced treatment groups in relation to an important risk factor for the outcome(s) of interest.

Exclusively hydrolysed formula: cow's milk formula described in original publication as extensively hydrolysed.

GRADE evaluation of evidence: grade of evidence in this report is assigned using the GRADE system, which has 4 categories HIGH, MODERATE, LOW or VERY LOW. Evidence is initially assigned as HIGH if coming from a randomised trial; LOW from observational studies; VERY LOW from other evidence. The grade of evidence is then reduced if there are serious (-1) or very serious (-2) limitations to study quality or uncertainties about directness of association; important inconsistency (-1), imprecise or sparse data (-1) or a high probability of reporting bias (-1). Grade of evidence is increased if strong evidence of association is seen (eg RR >2 or <0.5) from ≥2 observational studies with no plausible confounders (+1) or very strong direct evidence (RR >5 or <0.2) with no major threats to validity (+2); if there is evidence of a dose-response gradient (+1) or if all plausible confounders would have reduced the effect/association seen (+1). The interpretation of GRADE evidence assessments is that for HIGH level evidence further research is very unlikely to change our confidence in the estimate of effect; for MODERATE evidence further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; for LOW level evidence further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and for VERY LOW level evidence any estimate of effect is very uncertain. Further detailed explanation of GRADE can be found at :
http://www.gradeworkinggroup.org/publications/Grading_evidence_and_recommendations_BMJ.pdf

Partially hydrolysed formula: cow's milk formula described in original publication as partially hydrolysed.

qRCT: Quasi-randomised controlled trial. An intervention trial which used a predicatble allocation sequence, but one that was unlikely to lead to imbalanced treatment groups.
RCT: Randomised controlled trial. An intervention trial which reported that a random method of treatment allocation was used.

1.4. Methodology

The systematic review was undertaken according to PRISMA guidelines for intervention trial evidence, and MOOSE guidance for observational studies. The systematic review protocol was registered on PROSPERO. Studies included in the review were those relevant to infant use of hydrolysed formula, and allergic and autoimmune outcomes as described in more detail below.

1.4.1. Inclusion Criteria

a) Types of study included

We included recent high quality systematic reviews published from 2011 until the search date (25th July 2013; updated on 17th April 2015). Older systematic reviews were not included, due to the likelihood of being out of date. We quality assessed eligible systematic reviews using the revised AMSTAR criteria (12) and extracted data from systematic reviews with revised AMSTAR score ≥32. A summary of the identified reviews and data is included in the General Conclusions section at the end of this report.
We included original research studies published at any time prior to the search date (25th July 2013; updated on 17th April 2015 for intervention trials only). Original studies eligible for inclusion were randomised controlled trials (RCT), quasi RCT (RCT where the allocation sequence was predictable but not thought likely to lead to imbalance), controlled clinical trials (CCT where the allocation sequence was predictable, and thought likely to lead to significant imbalance between groups in important risk factors for the outcome(s) of interest), prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies, other case control studies and cross-sectional surveys. We took a hierarchical approach to study design, such that where data were absent or limited from systematic reviews or intervention trials, we included observational study data. Where a large number of intervention trials were identified, we did not analyse data from observations studies that assessed the same intervention/exposure. We did not

include non-comparative studies, or non-human studies. For this report, a large number of intervention trials were reported so observational studies were not analysed.

b) Participants/population

Inclusion criteria: Infants between birth and the end of their 12th post-partum month. If infants were characterised as high or normal/low risk for atopic or autoimmune disease based on family history or genotype, this information was be recorded so that it could be used for the planned subgroup analysis by disease risk.

Exclusion criteria: We excluded studies in which participants were defined by a disease state - eg pregnant women with specific nutritional deficiencies, infants born prematurely (<31 weeks gestation) or other groups clearly representing <5% of the UK population, since the results of this review should apply to the general UK population. We did not exclude studies on the basis of including specific ethnic groups, studies of high risk infants, since this applies to many UK-born infants for allergic disease, and it is difficult to undertake studies of autoimmune disease prevention in the general population without stratifying by genetic/family risk due to the relatively low prevalence of autoimmune diseases.

c) Interventions/ exposures

Exposures of interest in this report were:

(i). any extensively hydrolysed formula (eHF)

(ii). any partially hydrolysed (pHF)

(iii). any whey based hydrolysed formula

(iv). any casein based hydrolysed formula

(v). whey based eHF (w-eHF)

(vi). casein based eHF (c-eHF)

(vii). whey based pHF (w-pHF)

(viii). casein based pHF (c-pHF)

(ix). hydrolysed cow's milk formula not otherwise defined

Hydrolysed soy based formula, rice based formula or other non-cow's milk infant formula were not evaluated, but we planned to include other hydrolysed mammalian milk formulae eg hydrolysed goat milk or sheep milk formula if such studies were identified.

Comparators of interest were breast milk, whether given naturally, expressed and fed using a bottle, or from a donor mother; and non-hydrolysed cow's milk formula (or other mammalian milk formulae where relevant) including 'formula' or 'bottle feeding' not otherwise defined.

d) Study outcomes

We selected atopic and autoimmune outcomes on the basis of their population prevalence in children and young adults in the UK. We included diseases with a prevalence of at least 1 in 1000, in children/adolescents or young adults (aged <40 years), but did not include rarer diseases (13). We did not include pernicious anaemia or adult-onset rheumatoid arthritis despite a high prevalence in middle aged or elderly people, because their prevalence in young people is lower than 1 in 1000, and prospective studies of infant feeding in relation to diseases of older adults are unlikely to have been undertaken. We did not specifically exclude rare manifestations of food allergy such as eosinophilic oesophagitis, if they were reported as part of a food allergy definition, but did exclude them if they were reported as a unique outcome measure since their prevalence is less than 1 in 1000. For atopic outcomes, age at assessment was grouped as 1-4 years, 5-14 years, 15-24 years, 25-44 years, 45-64 years and ≥65 years. Due to a paucity of studies in adults, we pooled all age groups ≥ 15 years for almost all reports. For autoimmune outcomes, we did not stratify analyses by age at outcome assessment. Where studies reported the same outcome at different timepoints within one of these frames, we used the timepoint with the most complete dataset ie lowest percentage of missing data, as the primary assessment point for inclusion in meta-analysis. Where possible we chose a timepoint for outcome assessment that did not fall within the relevant exposure period ie the first year of life. For each outcome measure in this review, there is more than one possible method of assessment. We therefore included our preferred methods of assessment for each outcome as below *a priori*. In general where multiple measures of the same outcome were reported we selected outcomes that included the most complete data, used a published or validated assessment tool, and were meaningful for patients eg patient/parent-reported measures.

e) Atopic outcomes:

1. *Asthma/Wheeze* - defined as either 'asthma', 'infantile wheeze' or similar, using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure such as bronchial hyper-reactivity, forced vital capacity, peak expiratory flow rate or reversible airways obstruction using forced expiratory volume in 1 second. We included data for 'atopic' asthma/wheeze ie wheeze associated with allergic sensitisation, and for recurrent wheezing and atopic recurrent wheezing. We did not include different wheezing entities based on the timing of onset/resolution of the disease such as 'early transient wheeze' or 'persistent wheeze' due to heterogeneity in definition between studies. We did not include outcomes such as 'bronchitis' or 'bronchiolitis' which included some subjects with wheezing but others without wheezing.
2. *Eczema* – defined using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure. We included data for 'atopic' eczema ie eczema associated with allergic sensitisation. We did not include reports of rashes which were likely to have included other cutaneous problems, such as nappy rash, contact dermatitis, 'rash', 'skin problem' etc, but did include reports of 'recurrent itchy rash in infancy' or similar descriptions which were likely to represent eczema.
3. *Allergic Rhinoconjunctivitis* – defined using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure. We included data for 'atopic' rhinoconjunctivitis ie rhinoconjunctivitis associated with allergic sensitisation. We included data for 'allergic rhinitis', 'allergic conjunctivitis' or 'allergic rhinoconjunctivitis' and planned to analyse 'allergic conjunctivitis' separately where data were reported separately.
4. *Food allergy* - defined by double blind placebo controlled food challenge, by open food challenge, by medical diagnosis or by self/parent report. We included reports of 'any food allergy', and specific food allergies to cow's milk, egg or peanut. We did not include reports of 'food intolerance' that we judged were unlikely to meet current definitions of food allergy (14).
6. *Allergic sensitisation* – to an inhalant, an ingestant, or both – defined as positive skin prick test and/or specific IgE test to the relevant allergen using recognised methodologies and scoring criteria (15). We combined data for skin prick and specific IgE testing (using SPT where both were reported in the same study) due to limited numbers of studies available for each meta-analysis, and assessed 'any allergic sensitisation', 'food allergic sensitisation', 'aeroallergen sensitisation', 'cow's milk sensitisation', 'egg sensitisation' and 'peanut sensitisation' separately. We included Total IgE data when measured using a recognised technology such as ImmunoCAP (ThermoFisher, Massachusets).

f) Autoimmune outcomes:

1. *Type I diabetes mellitus* – defined as a medical diagnosis eg using the 1999 WHO recommendations for diagnosis and classification of diabetes mellitus (16), or a surrogate marker such as autoantibodies against insulin, GAD65, IA-2 or the ZnT8 transporter in the first 3 years of life. We did not include reports where the outcome was stated as 'diabetes' and thought likely to include some cases of type II diabetes mellitus or other disease entities.
2. *Coeliac disease* – defined by characteristic histological features (intraepithelial lymphocytes, crypt hyperplasia and villous atrophy) with improvement in symptoms and histology after institution of a gluten free diet, a medical diagnosis, or a surrogate marker such as IgA tissue transglutaminase or IgA endomysial antibodies.
3. *Inflammatory bowel disease* (Crohn's disease or Ulcerative colitis) – defined as a medical diagnosis.
4. *Autoimmune thyroid disease* (Graves' disease or Hashimoto's thyroiditis) - defined as a medical diagnosis.
5. *Juvenile rheumatoid arthritis* – defined as a medical diagnosis eg using the 2001 revised International League of Associations for Rheumatology (ILAR) classification criteria (17).
6. *Vitiligo* - defined as a medical diagnosis.

Primary assessment: medical diagnosis using the Vitiligo European Task Force 2007 criteria or similar (18).

7. *Psoriasis* - defined as a medical diagnosis.

1.4.2. Search strategy

The search strategies included both text terms and subject heading terms where appropriate. The search strategies were initially developed for use on the MEDLINE database and then adapted for use on other databases. We searched the following databases, with no specified start date:

- The Cochrane Library (2013, Issue 7)
- EMBASE (1947 to July 2013)
- LILACS (1982 to July 2013)
- MEDLINE (1946 to July 2013)
- Web of Science (1970 to July 2013)

The search was run on 25th July 2013 and included all studies published up to that date, and was updated on 17th April 2015 for intervention trials and systematic reviews. We included peer reviewed publications, and abstract publications if they contained data that had not subsequently been published as a peer reviewed publication. We reviewed the bibliography of eligible studies for possible additional publications, and included all eligible publications, regardless of the language. We did not contact the authors of eligible or potentially eligible studies to request original data. The search strategies were extensively piloted and refined to optimise sensitivity, comparing search results with those of other high quality published systematic reviews. The final search strategies for review C are included at the end of this report as *Appendices*.

The search for existing systematic reviews which cover any of the same exposure(s)/outcome(s) as the original studies was limited to publications from 1st January 2011 to 25th July 2013 in the original search, and to 17th April 2015 in the update. The search strategy was partly based on the search strategies used for Review A, Review B and Review C but included a search filter for retrieving systematic reviews (19). Open Grey was searched using the terms '(breast OR lactation OR formula) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to Review A; the terms '(wean OR peanut OR egg OR milk OR soya OR nut OR fish OR wheat) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to review B; the terms '(lactation OR pregnancy OR infant OR mother) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to review C.
The International Prospective Register of Systematic Reviews (PROSPERO) database was also searched for relevant systematic reviews. Due to the limited functionality of this resource individual keywords with date limits were used to search PROSPERO: we searched for titles containing 'breast OR infant OR lactation OR wean OR infant' for studies relevant to review A; 'nut OR wheat OR egg OR food OR diet' for studies relevant to review B; 'pregnant OR infant OR diet OR nutrition OR supplement' for studies relevant to review C.
The citations identified in searches were imported into Endnote libraries for de-duplication and title screening.

1.4.3. Study selection, data extraction and analysis

a) Study selection

Title and abstract screening was undertaken in duplicate by a team of 7 researchers (RB, VGL, DI, NG, KJ, JC, ZR). Two researchers undertook title screening independently, and met to agree included and excluded titles. Their screening was checked by a third member of the team, and uncertainties were brought to a full team meeting for discussion. This procedure took place between February and April 2014, with weekly team meetings to discuss uncertainties about study eligibility, and again in April 2015. The full text of all potentially eligible studies was reviewed, and where electronic copies were not available, hard copies of articles were ordered from the British Library.

b) Data extraction

An Excel data extraction form was developed, piloted and refined by DI, VGL, RB and JL-B – separate forms were used for intervention studies, cohort studies and case control studies. Data extraction was undertaken in duplicate by a team of 8 researchers (DI, RB, UN, SC, VGL, NT-M, NG, EA). Disagreements and uncertainties about data coding were discussed within the team with leads as follows - RB (clinical queries), VGLA (dietetic queries), DI (analysis and coding queries) and JL-B (study design and statistics queries). For foreign language studies, data were extracted by VGL together with a native speaker of the relevant language (see Acknowledgements section). We extracted all relevant data from included studies, including data that could not (not appropriately reported) or would not (see 'data cleaning' below) be included in meta-analysis, text information such as 'no significant association found', and information that adjusted or unadjusted analyses were performed but not reported.

c) Data cleaning and coding

Data were extensively cleaned and coded for analysis with further data checks to identify publications related to the same parent study, and to identify the most appropriate output for inclusion in meta-analysis from studies reporting multiple assessments of closely related exposures/outcomes at the same age in the same population. In general from individual studies reporting more than one measure for the same outcome, we selected data for analysis reporting time to event (hazard ratio) in preference to cumulative incidence or lifetime prevalence ie

'disease ever', in turn in preference to point prevalence data ie 'disease in the last 12 months' for all binary outcomes with the exception of the non-clinical outcomes allergic sensitisation and lung function, where point prevalence was analysed in preference to cumulative measures. Data cleaning was undertaken by DI, TK and RJB. The outcomes of both meta-analysed and narratively reported studies were considered together when interpreting data and making conclusions.

For allergic outcomes we grouped studies reporting outcome at ages 0-4, 5-15 and 15+ years. If a study reported associations (within or between publications) at more than one age within the same age group (ie age 1 and 3 years), we selected data for analysis within specific age groups that were most complete ie had the largest number of participants assessed. We also included data from longitudinal models (eg generalised estimating equation), and they were grouped according to the last age included in the model. Where appropriate we also considered the outcomes reported at other ages which were not included in meta-analysis, in our interpretation of the data. Age groups were not used for autoimmune diseases. Where different methods of outcome assessment were used within a study we prioritised validated and patient-centred outcomes – for example we prioritised clinical diagnosis of diabetes over diabetes-associated autoantibody detection; we prioritised patient or parent-reported wheeze using a validated instrument such as the ISAAC questionnaire, over doctor diagnosis of wheeze or study physician assessment. Again where appropriate the impact of these decisions was taken into account in our interpretation of findings.

For included studies which did not report numerical data in a form that could be included in meta-analysis, for example medians, or means without a standard deviation or standard error, or 'no significant difference' statements, we summarised the findings narratively in the text of the review.

d) Risk of bias assessment

Review level bias

Publication bias was assessed using funnel plots and Egger's test, for those meta-analyses with ≥10 studies included. Possible causes for asymmetry other than publication bias (eg between study heterogeneity, small study effects) were also considered. We also took into consideration both the outcomes of meta-analyses and the findings of studies not included in meta-analysis, when interpreting systematic review outcomes.

Study level bias

The risk of bias in included intervention studies was assessed using a modified version of the Cochrane Collaboration Risk of Bias tool, which assessed sequence generation and allocation concealment (Selection Bias), blinding of outcome assessors and validity of outcome assessment tool (Assessment Bias), incomplete outcome data (Attrition Bias – considered high where <70% of randomised participants had outcome data available). RCTs were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains selection, assessment and attrition bias. We assessed risk of Conflict of Interest as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors receive remuneration from relevant industry partners for other activities. The summary Risk of Bias Figures show the risk of bias for all studies reporting the relevant outcome, whether or not their data could be included in meta-analyses.

e) Strategy for data synthesis

Meta-analysis was undertaken where ≥2 studies reported the same outcome for a given exposure. Where meta-analysis was deemed inappropriate due to differences in population, exposure/intervention or outcome; or where meta-analysis was not possible due to the nature of the data reported - individual study results were summarised in a narrative table at the end of each report. Separate analyses were undertaken for each disease outcome, for each (age) group of similar outcome assessment methods for any given disease, and for each intervention/exposure (group). In general our approach to meta-analysis was inclusive, with data pooled for maximum statistical power, but explored for important sources of statistical or clinical heterogeneity. Results for randomised or quasi-randomised controlled trials were pooled separately from controlled clinical trials.

f) Data extraction

Where studies reported data at multiple timepoints within one of our pre-defined age groupings, we extracted the most complete dataset available, beyond the intervention period (ie from 1 year of age onwards). This is the dataset with the largest denominator, or where the denominator is identical for multiple time points then the largest numerator (number of events) is used. The GINI study (von Berg) used Generalized Estimating Equation (GEE) to generate Odds Ratios (OR) in some of their publications. This represents the most complete data available from the study, so

was selected in preference to other GINI study data analyses. Raw data or risk ratio (RR) were not given in the GEE reports. So for analyses which include GEE data from the GINI study we calculated odds ratio (OR) in place of RR in order to be able to include the most complete GINI study data available in meta-analysis. For some outcomes GEE data were not available from the GINI trial, and in these meta-analyses the most complete non-GEE data available were used. We planned to undertake subgroup/stratified analyses for meta-analyses which contained a total of >5 studies, and to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis.

g) Heterogeneity

Heterogeneity was quantified using I^2. We explored reasons for heterogeneity using subgroup analyses based on study level factors. We classified heterogeneity as low (I^2<25%), moderate (I^2 25-50%), high (I^2 50-75%) or extreme (I^2>75%). For single study analyses, and where I^2 exceeded 80% we did not pool data in meta-analysis but presented studies in a forest plot without a pooled effect shown. Individual patient data analysis was not undertaken in this review, and study authors were not contacted to clarify data queries or request further participant data.

h) Data analysis

Pooled results for binary outcomes from intervention studies are presented as RR calculated from the frequencies given in the study, or OR where appropriate as described above under 1.4.7. Data from individual studies were pooled using the generic inverse variance method for pooled OR and Mantel-Haenszel method (with continuity correction of 0.5 in studies with zero cell frequencies) or inverse variance method for single studies calculation of pooled RR in the statistical programme R version 3.1.0 (www.r-project.org). Pooled results for continuous outcomes measured using similar scales are presented as mean differences with 95% confidence intervals.

i) Planned subgroup analyses

We planned certain subgroup and stratified analyses prior to running our search. Subgroup analysis was undertaken for all meta-analyses with ≥ 6 studies included. We undertook planned subgroup analyses according to:

1. *Risk of bias* – studies with low, versus unclear/high overall risk of bias based on the criteria described above.

2. *Disease risk* - studies of populations at increased risk for atopic or autoimmune disease, versus those at normal or low risk of disease.
3. *Study design* – we also included a subgroup analysis for qRCT versus RCT.

In the Allergic Sensitisation meta-analyses we planned a stratified analysis of specific IgE (sIgE) versus Skin Prick Test (SPT) as outcome measure – this included all sIgE data and all SPT data for any given analysis, including data from studies which reported both sIgE and SPT outcomes from the same population. Hence a test for subgroup difference was not applied to this analysis.

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j) Graphical exploration of heterogeneity

Studies were ordered by year of publication in forest plots, in order to be able to assess any cohort effect, since the composition of infant formula and the prevalence of allergic and autoimmune diseases appear to have changed over time. Due to insufficient information in included studies, it was not possible to order forest plots by year of birth for the study population or year of assessment.

k) Review registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42013003802; CRD42013004239; CRD42013004252; www.crd.york.ac.uk/Prospero) on the 5th August 2013, prior to title screening or selecting any studies from the search results. The protocol was revised following detailed review by the UK Food Standards Agency, the UK Scientific Advisory Committee on Nutrition, independent experts Professor Graham Devereux and Dr Carina Venter, and the Lancet peer review service, prior to being registered on PROSPERO.

1.4.4. Differences between the protocol and review

Following external statistical review of preliminary reports, a decision was made to not undertake pooled meta-analysis where statistical heterogeneity was ≥80%. Due to insufficient data in included studies, we did not order forest plots by participant year of birth or year of outcome assessment. Instead we ordered by year of publication. New authors joined the review team due to the high workload of title screening and data extraction – TA, TK, SC, NG, ZR, JC, KJ, EA.

2. Executive summary: Hydrolysed formula and risk of allergic or autoimmune outcomes

2.1. Studies identified


PRISMA

Results of the study search are shown in this PRISMA flow chart:

In total we identified 37 intervention trials of hydrolysed formula, including over 19,000 participants. Overall there were 30 randomised controlled trials (RCT), 4 quasi-RCTs (qRCT) and 3 Controlled Clinical Trials (CCT) describing allergic or autoimmune outcomes. We classified studies as qRCT where the method of treatment allocation was not totally random, but was felt unlikely to lead to imbalance between treatment groups in variables relevant to the outcome measures. Where treatment allocation was non-random and likely to lead to significant imbalance between treatment groups, we classified studies as CCT and analysed them separately from RCT/qRCTs. All meta-analyses reported herein are for RCT/qRCT data, unless otherwise stated. Due to the large body of evidence from intervention trials, we did not extract data from the 5 observational studies identified, in keeping with the hierarchical approach to evidence synthesis outlined in the study protocol registered on PROSPERO reference CRD 42013004252 - weblink www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42013004252.

2.2. Populations

Twenty five studies were carried out in Europe, four in the USA, one in Canada, five in Asia, one in Australia and one in Europe/Asia/Australia. In 30 of 37 studies infants were at high risk of relevant outcomes. In 7 studies (Moran, Chan, Chirico, Porch, Willems, Vanderplas 1992, Scalabrin) the study population was unrepresentative of the general population due to very early formula feeding or refusal of mothers to breastfeed at all. In a further three studies (Dupont, Vanderplas 1988, Tsai) it was unclear whether or not the study population was similarly selected for a high rate of early formula feeding.

2.3. Interventions and comparators used

We included studies of any hydrolysed formula of cow's milk origin as the intervention of interest, and any non-hydrolysed cow's milk formula, human milk or another type of hydrolysed cow's milk formula as the comparators. We included studies where hydrolysed formula was given as part of a multifaceted intervention, and defined a multifaceted intervention as one with at least 2 other interventions in addition to the hydrolysed formula – for example maternal allergenic food exclusion, promotion of breastfeeding, delayed solid food introduction, or house dust mite avoidance measures. We included studies where other interventions were applied to both intervention and control groups, such as cow's milk avoidance during lactation. We did not include studies of hydrolysed formula of non-mammalian milk origin eg hydrolysed rice (nil identified) or soya formula (Isle of Wight study of Hide and Arshad).

Twenty three studies used partially hydrolysed formula (pHF) – always manufactured using the whey rather than the casein fraction of cow's milk. In at least 15 cases this was the Nestlé formula Nan HA/Good Start/Nidina HA/Beba HA. Eighteen studies used extensively hydrolysed formula (eHF), including one study comparing casein derived versus whey derived eHF, three studies comparing eHF with pHF and three studies assessing short term feeding in the first days of life, comparing eHF with cow's milk or human milk. Five studies used hydrolysed formula as part of a multifaceted intervention – usually including other measures during pregnancy, lactation or infancy such as allergenic food exclusion and delayed introduction of solid foods, and in two cases this included environmental control measures to reduce exposure to allergens such as house dust mite, and/or irritants such as cigarette smoke - CAPPS study (Chan-Yeung) and PREVASC study (Schonberger).

2.4. Outcomes evaluated

The outcomes eczema, wheeze (including lung function and bronchial hyper-responsiveness), allergic rhinitis, allergic conjunctivitis, allergic sensitisation, food allergy and type 1 diabetes mellitus were reported. We did not identify any studies reporting other autoimmune diseases as outcomes. Definitions used to assess the same outcomes varied across studies but largely used recognised assessment tools to define outcomes of interest. Age at outcome assessment was only at 0-4 years in 28 studies, and both ages 0-4 and ages 5-14 years in 9 studies. No study assessed outcomes beyond the age of 5-14 years.

2.5. Key Findings

i. Overall risk of bias was high or unclear in almost all studies, and for almost all outcomes

This was mainly due to poorly conducted or reported methods of randomisation. It is worth noting that 23 of the 37 trials were published before publication of the first CONSORT guidance (2001) for clinical trial reporting, and this may partly explain the poorly conducted or reported methods of randomisation. Almost all studies of allergic outcomes had a high or unclear risk of conflict of interest due to the level of probable or possible industry involvement in the trial, ie study sponsorship, employment of study authors, and/or consulting fees paid to study authors by a company with a commercial interest in the outcome of the trial. Studies of diabetes generally carried lower overall risk of bias, and low risk of conflict of interest due to independent study funding and investigators.

ii. We found evidence of publication bias in some analyses of allergic outcomes

Assessment of publication bias was undertaken for 4 analyses, which included >10 studies. In Funnel plots for eczema, and recurrent wheeze we found significant evidence of publication bias with Egger's test $P<0.05$. In one other Funnel plot for eczema and one for allergic sensitisation to cow's milk, we found no evidence of publication bias.

iii. We found no evidence that pHF or eHF prevent allergic outcomes or type 1 diabetes

Overall there was no evidence that the use of pHF or eHF reduces risk of eczema, wheeze, AR, food allergy or allergic sensitisation in 'high risk' children, and conclusions could not be drawn about effects in 'normal risk' children due to the very limited number of studies undertaken. We found no evidence that eHF reduces risk of type 1 diabetes mellitus (TIDM) in high risk children, compared with standard unhydrolysed cow's milk formula. We did not identify any studies of pHF and TIDM, or of hydrolysed formula and other autoimmune outcomes.

Table 1 Characteristics of included studies

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
Akerblom, 2005 (10) Knip, 2010 (20)	RCT	122/ 120	Finland	**TRIGR pilot**. Newborn infants with 1st degree relative with T1DM. High risk.	eHF-casein (Nutramigen, Mead Johnson) from <6 months to 6-8 months vs whey enriched CM formula (20% hydrolysed).	7, 8, 10	Diabetes Mellitus (clinical diagnosis, autoantibodies)
Akimoto, 1997 (21)	CCT	~35/~98	Japan	Newborn infants. Disease risk not stated	pHF-whey (Nan HA, Nestlé) from birth to 6 months if needed, vs standard infant formula	0.33, 1, 1.5, 3	Eczema (questionnaire survey), Wheeze (questionnaire survey)
Becker, 2004 (22); Chan-Yeung, 2000 (23); Chan-Yeung 2005 (24); Wong, 2013 (25)	RCT	281/ 268	Canada	**CAPPS Study.** Infants with family history of allergic conditions. High risk.	Multifaceted intervention including pHF-whey (Good Start, Nestlé) up to 12 months (only 8.3% of infants used), vs usual care/standard formula.	1, 7	Allergic Sensitisation (SPT), Allergic Rhinitis (DD), Wheeze (ISAAC and modified ECRHS), Eczema (DD), bronchial hyper-responsiveness (Metacholine PC20 <7.8), Lung function (FEV1)
Boyle 2015	RCT	432/431	Australia	**PATCH Study.**	pHF-whey (Nutricia)	1	AD (Hanifin and Rajka criteria)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
(26)			Singapore England and Ireland	Term infants with ≥one parent with allergic disease, and formula introduction <18 weeks. High risk.	+ prebiotic, vs standard formula, from <18 to 26 weeks. Outcome reported for those starting <4 wks.		
Chan, 2002 (27)	RCT	76/77	Singapore	Infants whose parents didn't intend to breastfeed/ atopy in a 1st degree relative. High risk.	pHF-whey (Nan HA) from birth to ≥4 months, vs standard formula.	0.3, 1, 2, 2.5	Wheeze (DD), Eczema (clinical diagnosis), Allergic Sensitisation (sIgE)
Chirico, 1997 (28)	RCT	Unclear. 21/14 assessed at 6 months	Italy	Very early formula introduction. Maternal history of atopy. High risk.	pHF-whey (Vivena HA, Plada) from birth to 6 months vs standard formula.	0.5	Allergic Sensitisation (sIgE), Eczema (clinical diagnosis)
de Seta, 1994 (29)	RCT	Unclear. 23/39 assessed at 2 years	Italy	Representative population of high risk infants. High risk.	pHF-whey (Nidina HA, Nestlé) with advice to delay CM introduction, vs standard formula from birth to 6	2	Eczema (Hanifin and Rajka criteria), Wheeze (DD)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
					months.		
Dupont, 2009 (30)	RCT	138/141	France	Multicentre study of high risk infants. High risk.	eHF vs pHF	1	Total IgE
Exl, 1998 (31)	qRCT	564/ 566	Switzerland.	**ZUFF Study.** Representative population. Normal risk.	pHF-whey (Beba HA, Nestlé) with solid foods delayed to 4 months, vs standard care.	0.1, 0.25, 0.5	Eczema (parental monitoring and DD), Wheeze
Halken, 1993 (32)	RCT	59/62	Denmark	High risk infants with raised cord blood IgE. High risk.	eHF-casein (Nutramigen) vs eHF-whey (Profylac), as needed to 6 months.	1.5	Eczema (DD), Wheeze (≥2 physician diagnosed episodes), Food allergy CM (food challenge)
Halken, 2000 (33)	qRCT	pHF 85; eHF-w 82; eHF-c 79	Denmark	High risk infants with raised cord blood IgE. High risk.	pHF-whey (Nan HA) vs eHF-casein or eHF-whey from birth to 4 months as needed.	1.5	Wheeze (≥3 physician diagnosed episodes), Eczema (DD), Allergic Rhinoconjunctivitis (DD), Food Allergy (Parental report/challenge)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
Juvonen, 1994 (34); Juvonen, 1996 (35); Juvonen, 1999 (36)	qRCT	~43eHF; ~58 HM, ~43 CM	Sweden	Healthy term infants. Normal risk.	eHF-casein (Nutramigen) vs standard formula or human milk, from 0 to 3 days. Exclusively breast-fed thereafter.	0.17, 0.33, 0.67, 2, 3,	Food Allergy (clinical symptoms), Eczema (physician assessment), Wheeze (physician assessment), Allergic Sensitisation (SPT, sIgE)
Knip, 2014 (37)	RCT	2613/2543	Finland	**TRIGR study.** Newborn infants with 1st degree relative with T1DM. High risk.	eHF-casein (Nutramigen) from <6 months to 6-8 months vs whey enriched CM formula (20% hydrolysed).	7	Diabetes Mellitus (>=2 or >=1 autoantibodies)
Lovegrove, 1994 (38)	RCT	12/14	UK	Allergic pregnant women aged 31 ± 5 years recruited. High risk.	Multifaceted intervention including eHF-whey (Peptijunior, Nutricia) vs standard formula/no intervention.	0.5, 1, 1.5	Eczema (DD)
Lowe, 2011 (39)	RCT	206/206	Australia	Representative population.1st degree relative with atopy. High Risk.	pHF-whey (Nan HA) vs standard formula during first year.	0.5, 1, 2, 7	Eczema (DD), Allergic Rhinitis (parental report/DD), Food Allergy (parent report), Wheeze (DD), Allergic Sensitisation (SPT)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
Mallet, 1992 (40)	RCT	92/85	France	Immediate family history of atopy. High Risk.	eHF-casein (Pregestimil, Mead Johnson) vs standard formula up to 4 months as needed.	0.33, 1, 2, 4	Wheeze (physician assessment), Eczema (physician assessment), Allergic Sensitisation (sIgE), Food Allergy (parent report)
Marini, 1996 (41)	RCT	80/75	Italy	Representative population. High Risk.	pHF-whey (Nidina HA) vs standard formula up to 5 months as needed.	1, 2, 3	Eczema (DD), Wheeze (≥3 physician diagnosed eposides) , Allergic Rhinoconjunctivitis (≥3 consecutive weeks of clinical symptoms)
Martikainen, 1996 (42); Vaarala,1998 (43)	RCT	10/10	Finland	Infants of mothers with diabetes. High Risk.	eHF-c (Nutramigen) vs standard formula, from < 6 until 9 months as needed.	0.5, 1	Diabetes Mellitus (clinical diagnosis, autoantibodies), Food Allergy
Moran, 1992 (44)	RCT	Unclear. 72/65 assessed at 8 months	USA	Term infants of mothers who elected not to breast feed. Mainly urban middle class families. Normal Risk.	pHF (Mead Johnson) vs standard formula, until 8 months.	0.67	Allergic Sensitisation (sIgE)
Nentwich, 2001 (45)	RCT	37/36	Czech Republic	Term infants with an allergic first degree relative. High Risk.	pHF-whey (Beba HA) vs eHF-whey (Hipp HA, Nutricia) for a mean 240 days	0.5, 1	Eczema (physician assessment), Allergic Sensitisation (sIgE)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
					in the first year.		
Odelram, 1996 (46)	RCT	~41/ ~41	Finland/ Sweden	Family history of atopy and raised cord blood IgE. High Risk.	eHF (Profylac, ALK) vs standard formula for the first year, as needed.	1.5	Food Allergy (physician assessment), Allergic Sensitisation (SPT, sIgE), Eczema (Seymour criteria), Allergic Rhinitis, Wheeze (≥2 physician diagnosed episodes)
Oldaeus,1997 (47); Oldaeus, 1999 (48)	RCT	51 pHF; 55 eHF; 49 CM	Sweden	Family history of atopy, raised cord blood IgE, maternal/infant milk/egg/fish exclusion. High Risk.	pHF (Mead Johnson) or eHF-casein (Nutramigen) vs standard formula, from weaning until 9 months.	0.75, 1, 1.5	Eczema (Seymour criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy (open food challenge), Wheeze (≥3 physician diagnosed episodes), Allergic Sensitisation (sIgE, SPT), Wheeze (parent reported)
Paronen, 2000 (49)	RCT	61/58	Finland	Newborn infants with 1st degree relative with TIDM, and high risk HLA type. High Risk.	eHF-casein (Nutramigen) vs standard formula, from <6 to 6-8 months as needed. Mean 4.8 months control/ 3.6 eHF.	2	Diabetes Mellitus (autoantibodies)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
Porch, 1998 (50)	RCT	59/48	USA	Formula fed from birth. At least one parent with allergy. High Risk.	pHF-whey (Good Start, Nestlé) vs eHF-casein (Nutramigen) for 1 year.	1	Eczema (DD/nurse diagnosed)
Saarinen, 1999 (51); Savilahti, 2009 (52)	qRCT	1737 eHF; 1789 CM; 1859 HM	Finland	Infants with formula milk before hospital discharge. Normal risk.	eHF-whey (Pepti-Junior) vs standard formula or human milk, from birth for mean 4 days.	2, 11.5	Food allergy - CM (food challenge), Diabetes Mellitus (clinical diagnosis)
Scalabrin, 2009 (53); Scalabrin, 2014 (54)	RCT	95/95	USA	Solely formula fed for ≥24 hours prior to 14 days age. Normal risk.	eHF-casein (Nutramigen) plus LGG vs pHF (Mead Johnson) with LGG, from <14 to 120-150 days age.	0.4, 5	Allergic Sensitisation (sIgE-CM), Eczema (DD), Wheeze (DD), Allergic Rhinitis (DD), Food Allergy (DD)
Schmitz, 1992 (55)	RCT	128/128	France	Representative population. Normal risk.	pHF-whey (Nidal HA, Nestlé) vs standard formula for the first 5 days of life.	0.25, 0.4, 1	Eczema (DD), Allergic Rhinitis (DD), Allergic Sensitisation (sIgE), Wheeze (DD)
Schonberger, 2005 (56)	RCT	242/234	Nether-lands	**PREVASC Study.** Mothers with family history of	Multifaceted intervention including eHF-whey	2	Eczema (ICHPPC), Wheeze (Dutch Guideline ‘‘Asthma in Children’’ and ISAAC), Allergic Sensitisation (sIgE)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
				asthma. High Risk.	(Nutrilon Pepti, Nutricia) vs standard advice/formula up to 6 months.		
Shao, 2006 (57)	RCT	23/23	China	Infants with family history of atopy. High Risk.	Multifaceted intervention including pHF-whey vs standard formula, from birth to 12 months.	1.5	Eczema (Wolkerstorfer score), Allergic Sensitisation (SPT)
Tsai, 1991 (58)	RCT	15/18	Taiwan	Healthy term infants at risk of of allergy. High Risk.	pHF-whey (Nan HA) from 1-2 to 6 months vs standard formula.	1	Eczema (clinical symptoms), Allergic Rhinitis (clinical symptoms), Wheeze, Allergic Sensitisation (sIgE)
Vaarala, 2012 (59)	RCT	350/389	Finland	**FINDIA Study.** Term infants with high risk HLA-type but no maternal diabetes. High risk.	eHF-whey (Peptidi-Tutteli, Valio) vs standard formula from birth to 6 months as needed.	0.25, 0.5, 3 , 6	Diabetes (autoantibodies, clinical diagnosis)
Vandenplas, 1988 (60)	qRCT	Unclear. 15/60 assessed at 4 months	Belgium	Infants at risk of allergy. ? not breastfed. High Risk.	Hypoallergenic formula (?pHF) vs standard formula up to 4 months.	0.33	Allergic Sensitisation (sIgE, SPT)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
Vandenplas 1992 (61); Vandenplas 1995 (62)	RCT	~38/~38	Belgium	Family history of atopy, and not breast fed. High Risk.	pHF-whey (Nan HA) vs standard formula, from birth to 6 months.	0.5, 1, 3	Eczema, Allergic Rhinoconjunctivitis (clinical symptoms), Wheeze (clinical symptoms), Allergic Sensitisation (sIgE, SPT), Food Allergy
von Berg 2003 (63), 2008 (64), 2010 (65), 2013 (66)	RCT	eHF-w 559; eHF-c 580; pHF-w 557; CM 556	Germany	**GINI Study.** First degree family member with allergic disease. Representative population. High Risk.	pHF-whey (Beba HA), eHF-casein (Nutramigen) or eHF-whey (Hipp HA) vs standard formula to 6 months as needed. 65% introduced formula <4 weeks.	1, 3, 6, 10	Eczema (Hanifin and Rajka criteria), Food Allergy - Any (IgE and non-IgE, clinical symptoms), Wheeze (parent reported ≥3 episodes), Allergic Sensitisation (sIgE)
Willems, 1993 (67)	CCT	~90/~90	Belgium	Infants who were not breastfed at all, with a first degree relative affected by allergy. High Risk.	pHF-whey (Nan-HA) vs standard formula, from birth to 3 months.	1	Eczema (DD), Wheeze (DD), Allergic Rhinoconjunctivitis (DD)
Han, 2003 (68)	CCT	~40/~40	South Korea	Healthy term infants of parents with allergic disease attending a Dairy Industry maternity school.	pHF (HA21, Maeil Dairy Industry) vs standard formula from birth to 6 months as needed.	0.5	Eczema

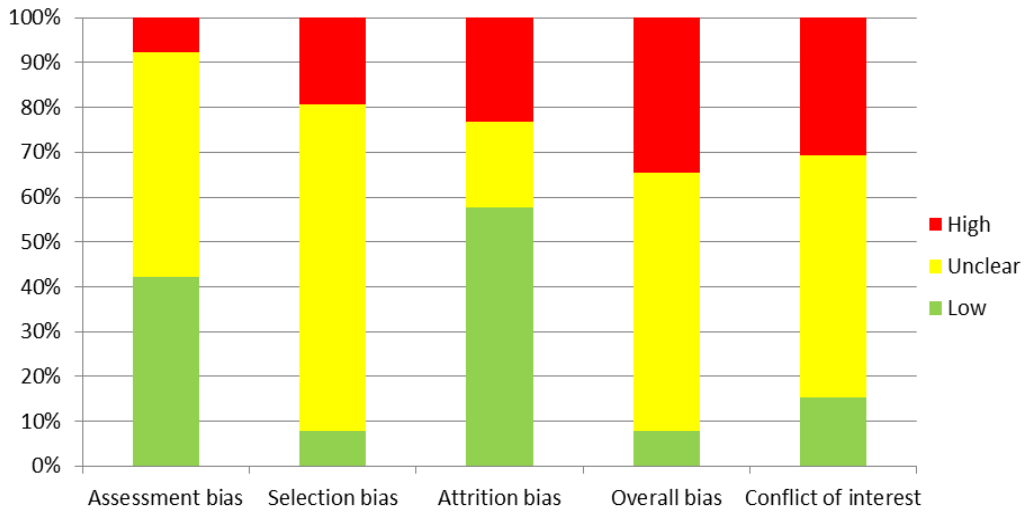
Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported with method of assessment
				High Risk.			
Zeiger 1989 (69), 1995 (70)	RCT	Unclear. 103/185 followed at 4 months	USA	Infants covered by Kaiser Permanente Health Plan, with an allergic parent. High Risk.	Multifaceted intervention including eHF-casein (Nutramigen), vs no intervention/standard formula as needed to 1 year.	2, 4, 7	Eczema (Hanifin and Rajka Criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy - Any (DD), Wheeze (≥2 physician diagnosed episodes), Allergic Sensitisation (SPT)

ICHPPC International Classification of Health Problems in Primary Care, RCT Randomised controlled trial, qRCT Quasi-randomised controlled trial, CCT Controlled Clinical Trial, DD Doctor diagnosis (community), Physician assessment is assessment by study physician, SPT skin prick test, sIgE specific IgE, CM cow's milk formula, HM human milk, pHF partially hydrolysed formula, eHF-c extensively hydrolysed, casein based formula, eHF-w extensively hydrolysed, whey based formula. Nan HA, Beba HA, Good Start, and Nidal HA are the same product with different brand names. Hipp HA and Nutrilon Pepti are the same product with different brand names.

3. Hydrolysed formula and risk of eczema

Twenty seven intervention studies investigated the effect of hydrolysed formula on risk of eczema in over 5000 participants. One third of studies were considered to be at high risk of bias, due to high attrition bias (>30% of randomised participants not analysed for the outcome) or high selection bias (inadequate randomisation, allocation concealment and/or imbalanced randomisation). Thirty per cent of studies had high risk of conflict of interest, due to direct industry involvement in the study design, analysis or publication (Figure 1).

Figure 1 Risk of bias in intervention studies of HF and eczema



3.1. pHF vs CM and risk of eczema in children aged 0-4 years

Eleven RCTs and one qRCT (Exl 1998) reported pHF vs CM and risk of eczema in children aged 0-4, shown in Figure 2. The pooled data show no significant effect on eczema risk, with moderate statistical heterogenenity (I^2 = 30%). Two CCT studies reported pHF vs CM and risk of eczema in children aged 0-4, shown in Figure 3. The pooled data show evidence of reduced risk of eczema with low heterogenitiy (I^2 = 16.2%). A Funnel plot to explore publication bias for the RCT/qRCT data is shown in Figure 4 and shows no evidence of publication bias (P=0.33). Subgroup analyses are shown in Table 2. There was evidence that study design or disease risk may be relevant to outcomes, with the single qRCT in a normal risk population (Exl 1998) showing a positive finding, but not the RCTs in high risk populations. When RCT/qRCT/CCT data were analysed together with a test for subgroup difference according to study design, there was strong evidence for difference (P=0.001) with increased treatment effect seen in CCT>qRCT>RCT. There was no evidence that

multifaceted intervention versus formula alone impacted on study outcomes, nor that the single study with low overall risk of bias (von Berg) had significantly different outcomes. All studies reporting eczema at age 0-4 had either high or unclear risk of conflict of interest.

Data not included in meta-analysis

The study of Vandenplas 1995 reported reduced eczema risk at age 6 months, but not at age 1 year (shown in Figure 2) or aged 3 years (Intervention 6/28; Control 6/30). The studies of Marini, Oldaeus, Exl, Chan and Akimoto reported eczema at several ages within the 0-4 age group. Findings were similar at all ages, within each study, and are represented by the data in the meta-analysis which are the most complete data reported from each study, beyond the age of 1 year. The GINI trial (von Berg) reported data for this outcome at age 3 which are GEE data, included in meta-analysis, and also reported data at age 1 year. The GINI 1 year analysis reported eczema in 22/241 pHF versus 38/256 control group infants (RR 0.61 95% CI 0.37-1.01), reported as statistically significant with adjusted OR 0.56 (95% CI 0.32, 0.99) in the publication. However this analysis excluded randomised participants who did not take up the intervention, or were poorly compliant with the intervention, so this was not intention to treat analysis, in contrast to the GINI 3 year data included in Figure 2. The study of Willemscould not be included in meta-analysis. They did not report data for individual outcomes comparing those randomised to pHF versus standard formula, although they did measure eczema risk at the age of 1.

Post-hoc subgroup analysis

At the suggestion of a reviewer, we undertook post-hoc subgroup analysis to evaluate whether Nestlé pHF-whey has different effects to other pHF-whey formula. This is relevant due to FDA approval of a limited health claim that Nestlé pHF reduces eczema risk in 2010, a decision based largely on Per Protocol analysis of von Berg's study (GINI), without the subsequent negative Nestlé pHF study of Lowe at al 2011 (71). Our post-hoc analysis showed no evidence for subgroup difference (p=0.27), with 9 Nestlé pHF studies finding OR for eczema 0.82 (95% CI 0.68, 1.00; I^2=34%), and 3 other pHF studies finding OR 1.02 (0.74, 1.41; I^2=17%). If the qRCT of Exl is excluded, pooled analysis of the Nestlé pHF RCTs shows OR 0.89 (0.68, 1.16) with reduced statistical heterogeneity I^2=13%.

Figure 2 pHF vs CM for preventing eczema at 0-4 years – RCT evidence

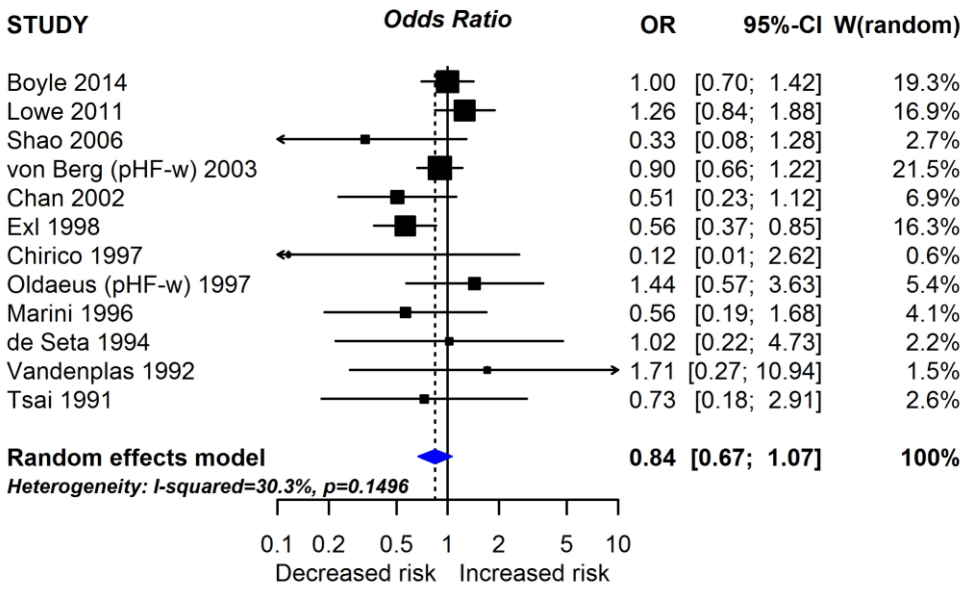


Figure 3 pHF vs CM for preventing eczema at 0-4 years - CCT evidence

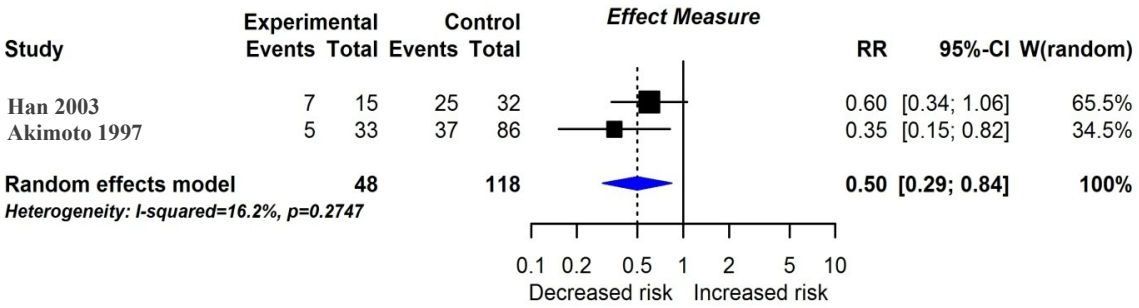
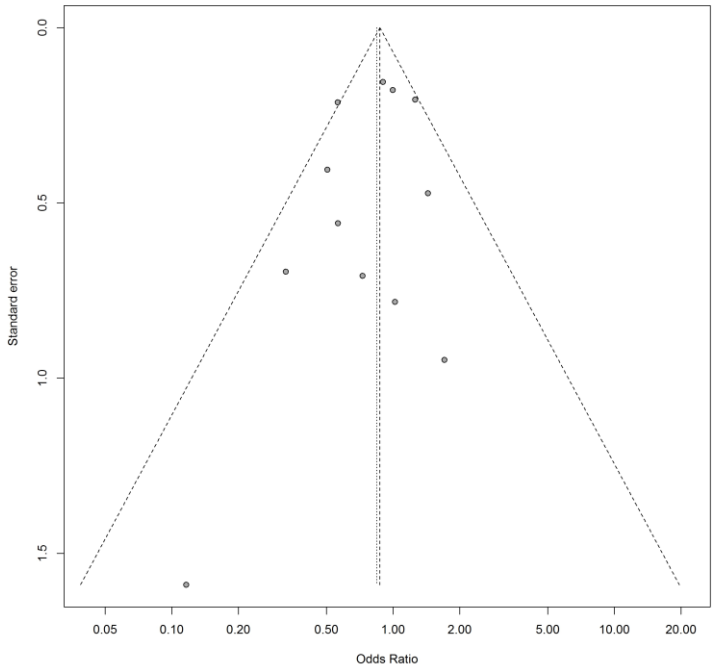


Figure 4 Funnel plot for pHF vs CM and risk of eczema at 0-4 years



Egger's test p-value = 0.33

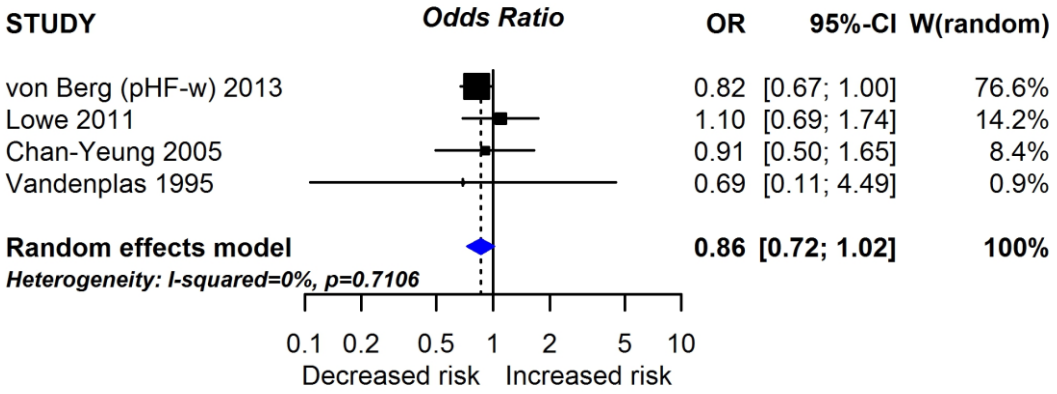
Table 2 Subgroup analysis of pHF vs CM and eczema risk in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	1	0.56 [0.37-0.85]	-	0.025
Design – RCT	11	0.95 [0.79-1.13]	7	
Risk of disease – High	11	0.95 [0.79-1.13]	7	0.025
Risk of disease – Normal/Low	1	0.56 [0.37-0.85]	-	
pHF type – Casein	0	-	-	-
pHF type – Whey	12	0.84 [0.67-1.07]	30	
Intervention protocol – Formula only	10	0.89 [0.75-1.05]	26	0.070
Intervention protocol – Multifaceted	2	0.28 [0.08-0.97]	0	
Overall risk of bias – Low	1	0.90 [0.66, 1.22]	-	0.65
Overall risk of bias – High/Unclear	11	0.81 [0.60-1.10]	36	
Conflict of interest bias – Low	0	-	-	-
Conflict of interest bias – High/Unclear	12	0.84 [0.67-1.07]	30	

3.2. pHF vs CM and risk of eczema in children at age 5-14

Four studies reported pHF vs CM and risk of eczema in children aged 5-14, shown in Figure 5. The pooled data show no evidence of reduced risk with no statistical heterogenenity (I^2 = 0%). The GINI trial (von Berg) reported this outcome at aged 10 using Generalized Estimating Equation (included in meta-analysis Figure 5) and at age 6. At age 6, the authors reported that pHF-w reduces eczema risk RR 0.79 (95%CI 0.64, 0.97). In the study of Chan-Yeung there was relatively little uptake of the pHF with only 8% of participants randomised to pHF actually using the formula.

Figure 5 pHF vs CM for preventing eczema at 5-14 years



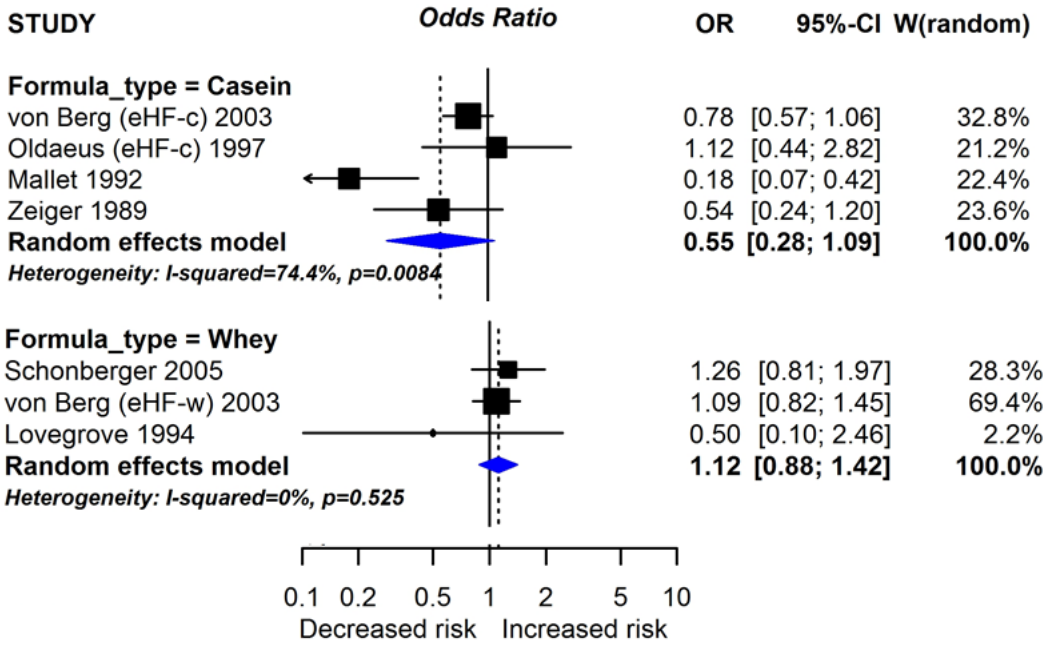
3.3. eHF vs CM and risk of eczema in children at age 0-4

Six studies with 7 interventions reported eHF vs CM and risk of eczema in children aged 0-4, shown in Figure 6. The pooled data for eHF-c and eHF-w show no reduced risk of eczema with high heterogenenity (I^2 = 74%) for eHF-c but no heterogeneity for eHF-w. One study (von Berg) had a low overall risk of bias, and no study had low risk of conflict of interest.

Data not included in meta-analysis

The studies of Oldaeus, and Zeiger reported eczema at more than one age within the 0-4 age group. Findings were similar at other ages, within each study, to the data in the meta-analysis which are the most complete data reported from each trial, beyond the age of 1 year. Lovegrove also reported a per protocol analysis excluding 3 infants who had a commercial formula in the intervention group by mistake, showed slightly more favourable numbers ie 2 at 1 year and 1 at 1.5 years with eczema in the intervention group. The study of Odelramwith ~80 participants randomised did not report any outcome data, although eczema was measured as an outcome. The study only reported data as 'any allergic disease' with 15/32 in the CM group and 10/25 in the eHF group. The GINI trial (von Berg) reported data for this outcome at the age of 3 using GEE (shown in Figure 6) and also at age 1 where they reported a significant reduction in eczema risk for eHF-c but not for eHF-w. At age 1 the data reported were not intention to treat ie they excluded participants who didn't take up the intervention or were poorly compliant with the intervention.

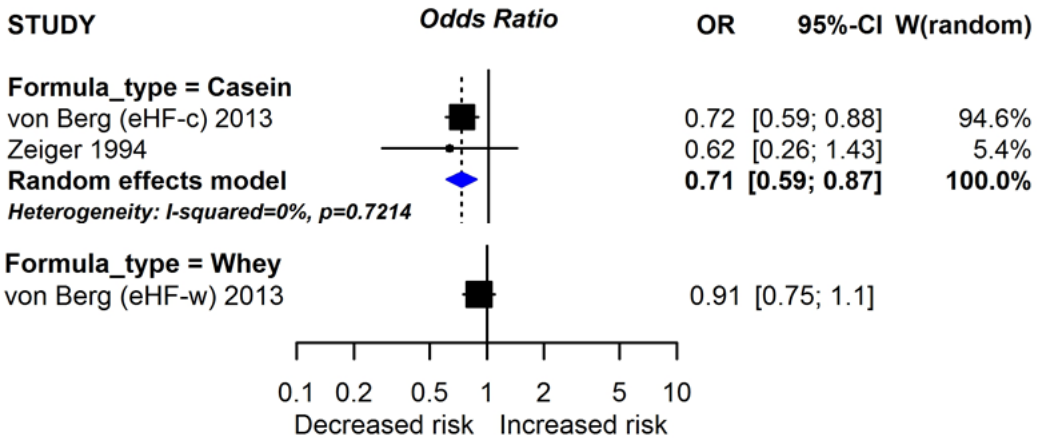
Figure 6 eHF vs CM for preventing eczema at 0-4 years



3.4. eHF vs CM and risk of eczema in children aged 5-14

Two studies with 3 interventions reported eHF vs CM and risk of eczema in children aged 5-14, shown in Figure 7. The pooled data show reduced risk of eczema with eHF-c, with no statistical heterogenenity (I^2 = 0%), but no effect for eHF-w. The GINI trial (von Berg) reported this outcome at aged 10 using GEE (included in meta-analysis) and at age 6. At age 6, there was also evidence that eHF-c reduces eczema risk RR 0.71 (95%CI 0.58, 0.88) but not eHF-w RR 0.92 (95% CI 0.76, 1.11). Zeiger reported cumulative incidence of eczema (shown in meta-analysis – derived from graphically presented data) and period prevalence of eczema at age 7. While cumulative incidence of eczema was slightly higher in the control group, period prevalence was almost identical between intervention and control groups.

Figure 7 eHF vs CM for preventing eczema at 5-14 years



3.5. Any HF vs CM and risk of eczema in children aged 0-4

In total 16 studies reported any HF vs CM and risk of eczema aged 0-4, shown in Figure 8. The pooled data show reduced risk of eczema with statistical significance but with high heterogenenity (I^2 = 53.3%). For this analysis GINI study (von Berg) GEE could not be used, so we used the next most complete data which had significant post-randomisation exclusions. A Funnel plot to explore publication bias is shown in Figure 9 and shows evidence of publication bias (Egger's test P=0.019), suggesting there may be unpublished negative trials.

Subgroup analyses are shown in Table 4. There was no evidence that study design, disease risk, multifaceted intervention versus formula alone, impacted on study outcomes. However there was some evidence that eHF-casein (eHF-c) may be more effective than pHF-whey or eHF-whey (eHF-w) in reducing eczema risk, albeit still with high statistical heterogeneity. All included studies carried high or unclear risk of bias and conflict of interest.

Figure 8 AnyHF vs CM for preventing eczema at 0-4 years

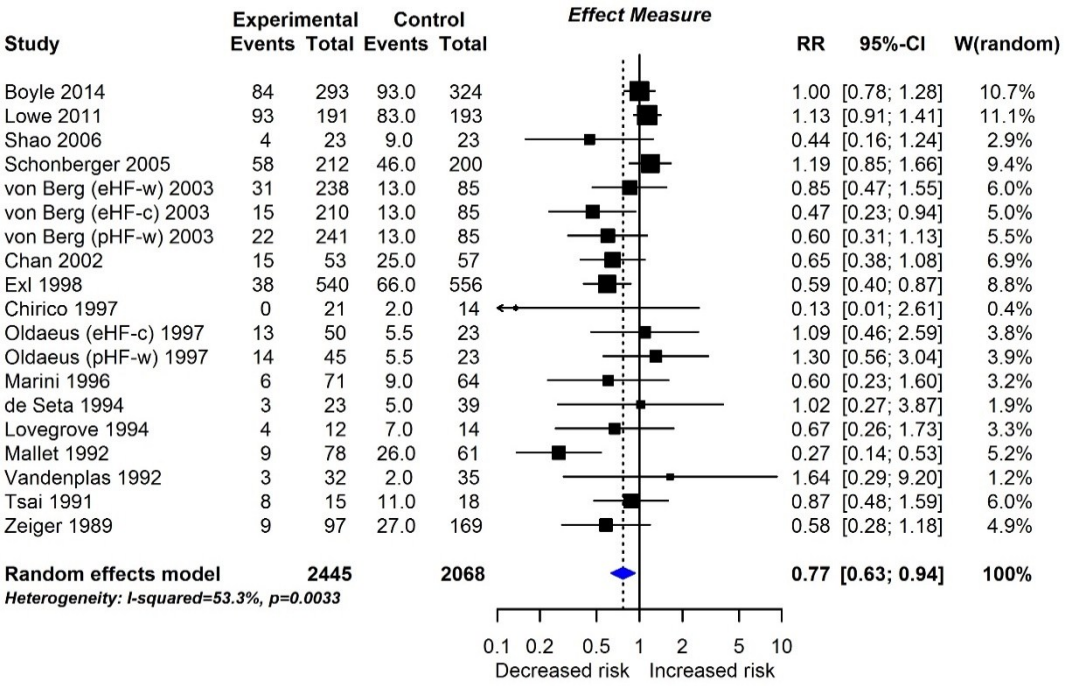
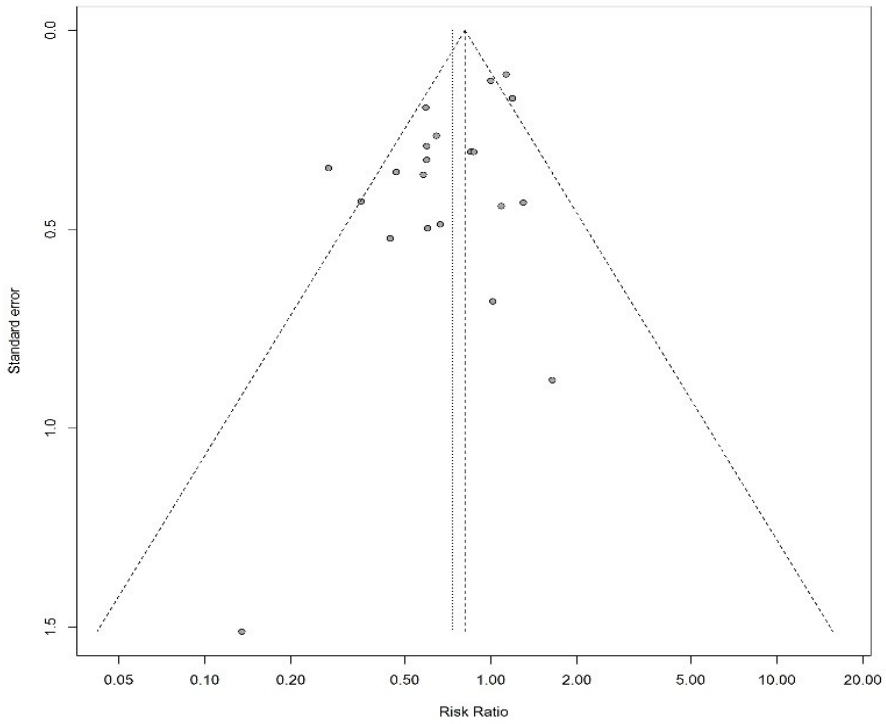


Figure 9 Funnel plot for any HF vs CM and risk of eczema at age 0-4



Egger's Test p-value = 0.019

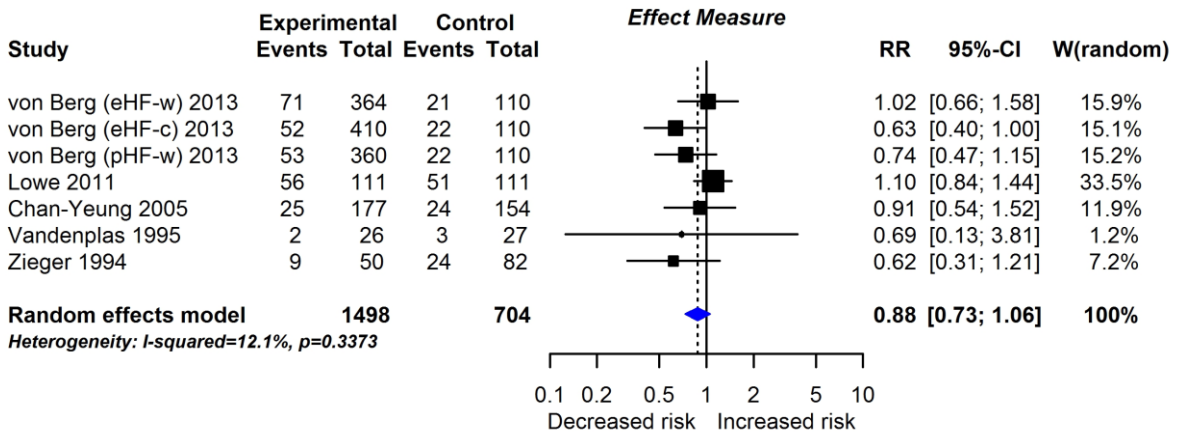
Table 3 Subgroup analysis of Any HF vs CM and risk of eczema in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	1	0.59 [0.40-0.87]	-	0.20
Design – RCT	18	0.79 [0.64-0.97]	49.7	
Risk of disease – High	18	0.79 [0.64-0.97]	49.7	0.20
Risk of disease – Normal/Low	1	0.59 [0.40-0.87]	-	
HF type – eHF-Casein	4	0.51 [0.30-0.87]	53.3	
HF type – eHF-whey	3	1.05 [0.80-1.39]	0	0.057
HF type – pHF-whey	12	0.83 [0.67-1.03]	40.1	
Intervention protocol – Formula	14	0.76 [0.61-0.96]	57.4	0.83
Intervention protocol – Multifaceted	5	0.71 [0.43-1.21]	49.4	
Overall risk of bias – Low	0	-	-	-
Overall risk of bias – High/Unclear	19	0.77 [0.63-0.94]	53.3	
Conflict of interest bias – Low	0	-	-	-
Conflict of interest bias – High/Unclear	19	0.77 [0.63-0.94]	53.3	

3.6. Any HF vs CM and risk of eczema in children age 5-14

In total five studies with 7 interventions reported any HF vs CM and risk of eczema aged 5-14, shown in Figure 10. The pooled data show no effect on risk of eczema with no statistical heterogenenity (I^2 = 0%). %). For this analysis GINI (von Berg) GEE could not be used, so we used the next most complete data which had significant post-randomisation exclusions. Most studies in this analysis used pHF rather than eHF, so we also ran an analysis using GINI (von Berg) GEE data for pHF but no eHF data, and found similar findings (OR 0.88 95% CI 0.72, 1.07; but with high heterogeneity I^2=72%).

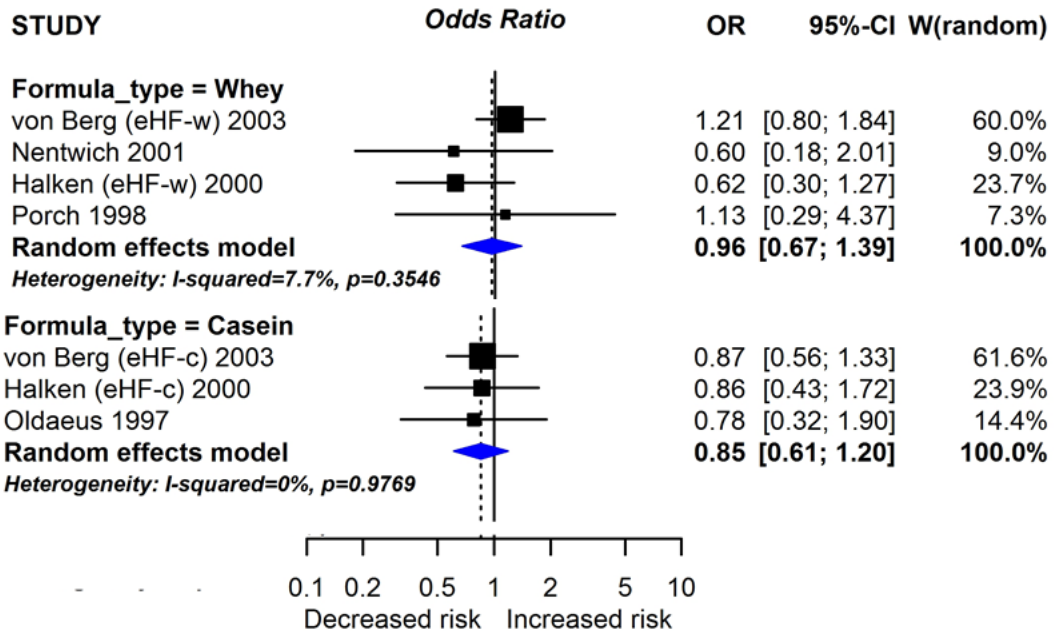
Figure 10 AnyHF vs CM for preventing eczema at 5-14 years



3.7. eHF vs pHF and risk of eczema in children aged 0-4

Five studies including 7 interventions reported eHF vs pHF and risk of eczema in children aged 0-4, shown in Figure 11. The pooled data show no evidence of difference in eczema risk, with low or no statistical heterogenenity for eHF-w and eHF-c respectively.

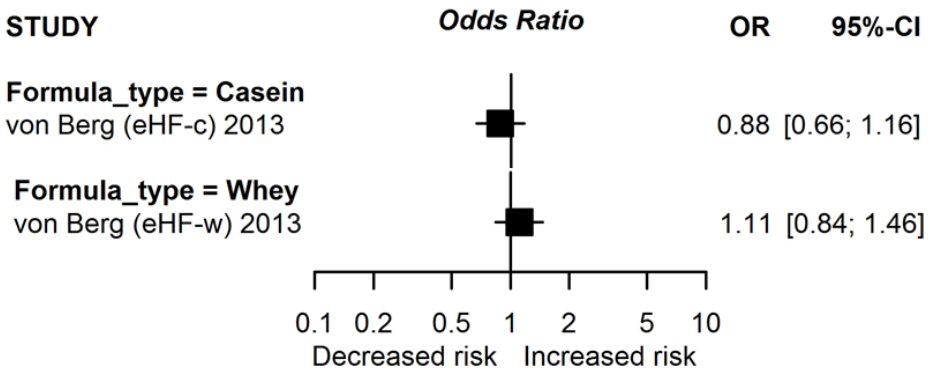
Figure 11 eHF vs pHF for preventing eczema at 0-4 years



3.8. eHF vs pHF and risk of eczema in children aged 5-14

One study with two interventions reported eHF vs pHF and risk of eczema at 5-14, shown in Figure 12. The data show no evidence of an effect for eHF-c or eHF-w. The study of Scalabrin also found no significant difference between groups in doctor diagnosed AD at age 5 years. They assessed 64 children randomised to eHF-c (half randomised to eHF-c with a probiotic), and 37 randomised to pHF at this age, but did not report numerical data that could be included in meta-analysis.

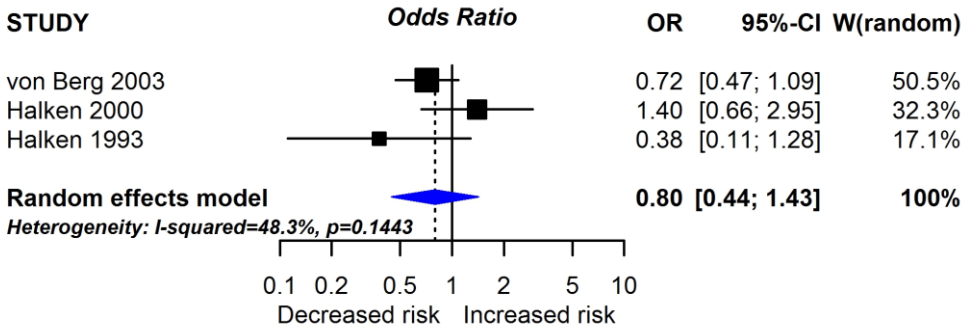
Figure 12 eHF vs pHF for preventing eczema at 5-14 years



3.9. eHF-c vs eHF-w and risk of eczema in children aged 0-4

Three studies reported eHF-c vs eHF-w and risk of eczema in children aged 0-4, shown in Figure 13. The pooled data show no evidence of difference in eczema risk, with moderate statistical heterogenenity ($I^2 = 48\%$).

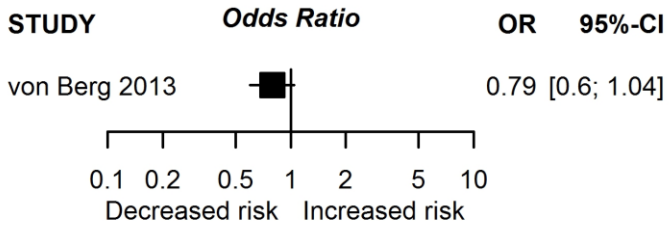
Figure 13 eHF-c vs eHF-w for preventing eczema at 0-4 years



3.10. eHF-c vs eHF-w and risk of eczema in children aged 5-14

One study reported eHF-c vs eHF-w and risk of eczema at 5-14, shown in Figure 14. There was no evidence of reduced risk of eczema with eHF-c compared with eHF-w.

Figure 14 eHF-c vs eHF-w for preventing eczema at 5-14 years



3.11. Short term HF in the first days of life, and risk of eczema in children aged 0-4

One study reported very short term use (0-3 days) of eHF vs standard cow's milk formula (CM; Figure 15) or human milk (HM; Figure 16) in relation to risk of eczema at 0-4. There was no evidence of reduced eczema risk with eHF, but confidence intervals were wide due to small study numbers. Schmitz used short term pHF compared with CM, and reported no significant difference between groups in eczema prevalence in the first year, but did not provide numerical data.

Figure 15 eHF vs CM_Short for preventing eczema at 0-4 years

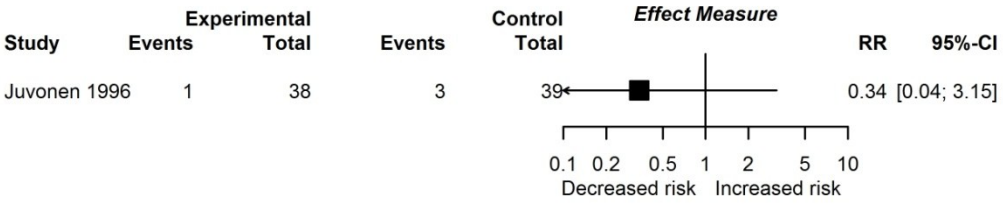
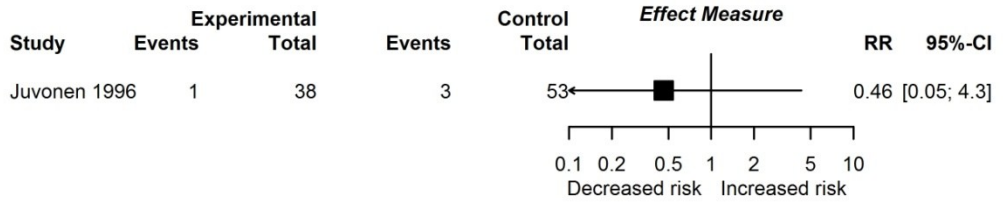


Figure 16 eHF vs HM_Short for preventing eczema at 0-4 years



3.12. Conclusions

These data were largely derived from studies with high or unclear risk of bias, and high or unclear risk of conflict of interest. All RCTs were conducted in children at high risk of allergic outcomes, so the evidence can only be considered relevant for high risk children.

There is no consistent evidence that the use of pHF in place of standard formula reduces the risk of eczema in children aged 0-4 or aged 5-14. In analysis of pHF and eczema at age 0-4, there was strong evidence that studies with inadequate methods of randomisation yielded more positive findings than those where the interventions were randomly allocated, and there was evidence of publication bias in studies of 'any HF' and eczema at age 0-4. Consistent with the evidence we found for publication bias, we identified studies which had recorded eczema as an outcome but did not present numerical data for this outcome, and we are aware of one unpublished HF trial for eczema prevention with no significant effect (personal communication, Professor Hasan Arshad).

We found some evidence that eHF-c (usually Nutramigen, Mead Johnson) may reduce eczema risk at age 5-14, compared with standard cow's milk formula, but did not find the same for eHF-w, and neither eHF-c nor eHF-w led to significantly reduced eczema at age 0-4. The finding that eHF-c may reduce eczema risk at age 5-14 was based largely on a single study GINI (von Berg) with a low selection and assessment bias risk, but high attrition bias risk due to 36% loss to follow up at 10 years, and unclear conflict of interest risk due to HF industry support of authors through speaker fees/ advisory boards/ research support.

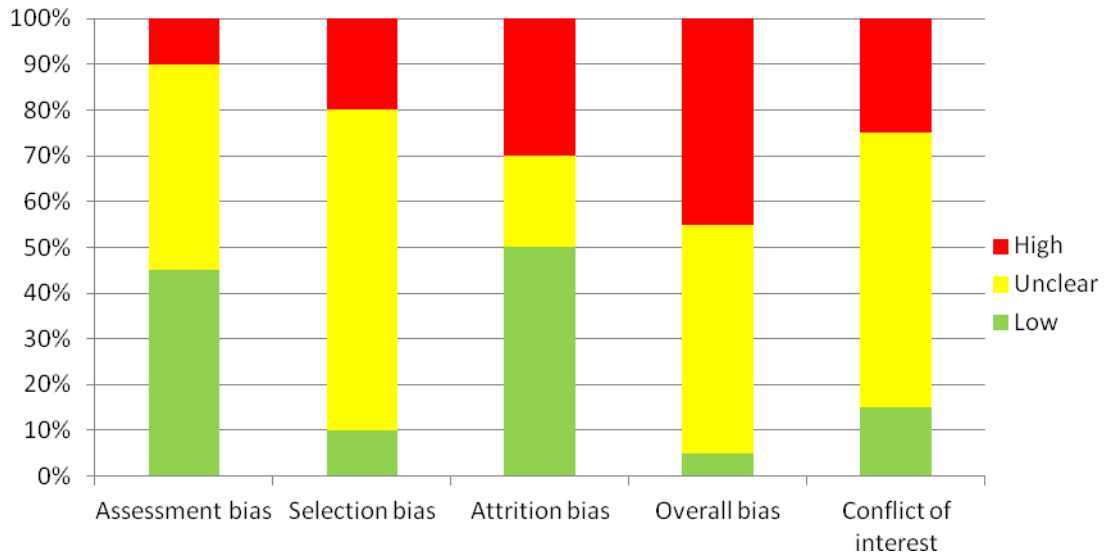
Separate analyses of eHF vs pHF or eHF-c vs eHF-w did not find significant differences. We found no evidence that short term feeding (0-3 days) with eHF in the first days of life has any advantage over either human milk or unhydrolysed formula milk, but these analyses were essentially inconclusive due to very small sample size.

Given the lack of studies with a low overall risk of bias and low risk of conflict of interest, the evidence of publication bias, and the lack of statistically significant findings in most analyses, we conclude that there is no evidence to support an association between infant feeding with a partially or extensively hydrolysed formula and reduced eczema risk.

4. Hydrolysed formula and risk of wheeze

Twenty one intervention studies investigated the effect of hydrolysed formula on risk of wheeze, recurrent wheeze or lung function changes, in over 7000 participants. Almost half of studies were considered to be at high risk of bias, due to high attrition bias (>30% of randomised participants not analysed for the outcome) or high selection bias (inadequate randomisation, allocation concealment and/or imbalanced randomisation). One quarter of studies had high risk of conflict of interest, due to direct industry involvement in the study design, analysis or publication (Figure 17).

Figure 17 Risk of bias in intervention studies of HF and Wheeze



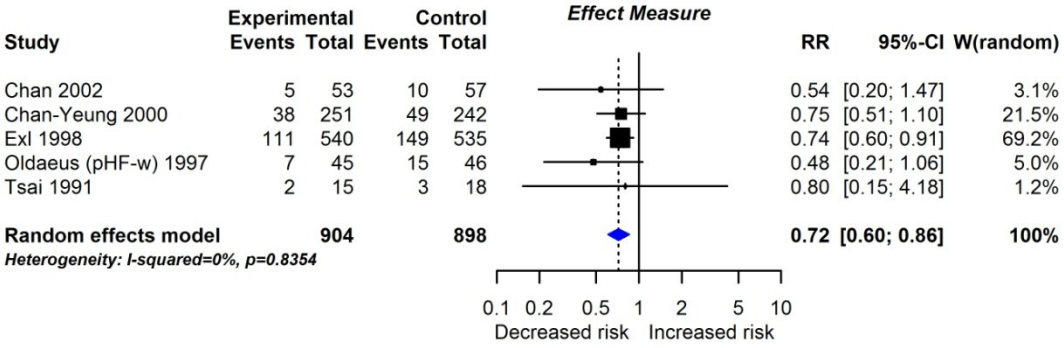
4.1. pHF vs CM and risk of wheeze in children at age 0-4

Five RCT or qRCTs reported pHF vs CM and risk of wheeze in children aged 0-4, shown in Figure 18. The pooled effect shows significantly reduced risk of wheeze with pHF, with no statistical heterogeneity ($I^2 = 0\%$). The analysis was dominated by a qRCT with high overall risk of bias and high risk of conflict of interest (Exl), and a multifaceted intervention trial in which only 8% of participants in the intervention arm used the pHF formula they were allocated to (Chan-Yeung). One small CCT with 124 participants assessed reported no wheezing in either treatment arm (Akimoto).

Data not included in meta-analysis

The studies of Chan and Oldaeus also reported data for this outcome at other ages, with similar findings. The study of Willems (n=67) measured the outcome of wheeze, but did not report the data. The study of Vandenplas1992 (n=67) reported no difference between groups in 'cough and other respiratory outcomes' at age 6 months.

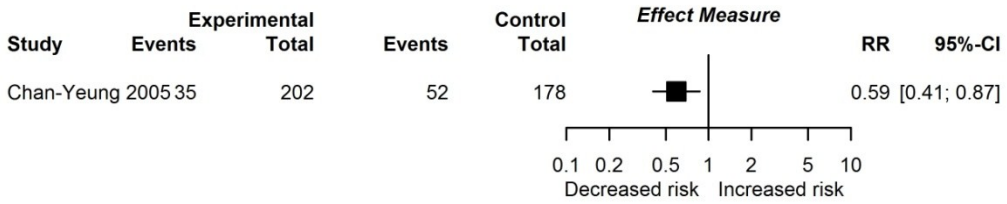
Figure 18 pHF vs CM for preventing wheeze at 0-4. RCT/qRCT evidence



4.2. pHF vs CM and risk of wheeze in children at age 5-14

One study reported pHF vs CM and risk of wheeze in children aged 5-14, shown in Figure 19. They found evidence of reduced risk of wheeze in children randomised to pHF, although it is worth noting that relatively few (8%) participants used the pHF in this multifaceted intervention trial.

Figure 19 pHF vs CM for preventing wheeze at 5-14 years

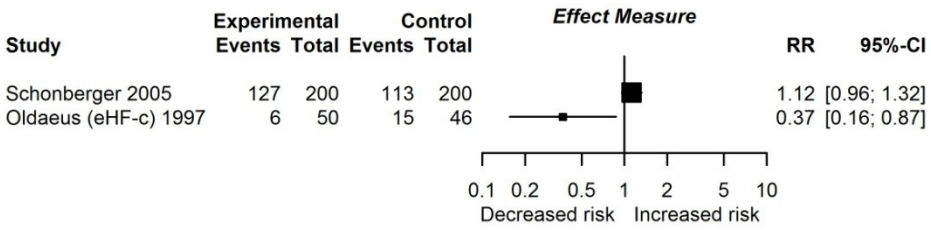


4.3. eHF vs CM and risk of wheeze in children at age 0-4

Two studies reported eHF vs CM and risk of wheeze in children aged 0-4, shown in Figure 20. Pooled data are not shown due to extreme statistical heterogeneity (>80%). The study of Shonberger reported no association between eHF treatment and wheeze at age 1 (in Figure

20), and also reported no association at age 2 OR 0.88 (95% CI 0.72-1.1). Oldaeus found eHF-c reduced wheezing at age 1 (shown in Figure 20), but reported no significant association at other ages.

Figure 20 eHF vs CM for preventing wheeze at 0-4 years



4.4. Any HF vs CM and risk of wheeze in children at age 0-4

Overall 6 studies reported AnyHF vs CM and risk of wheeze in children aged 0-4, shown in Figure 21. The pooled data show no clear evidence of reduced risk of wheeze, but with high heterogenenity (I^2 = 69.1%). Subgroup analyses are shown in Table 7. There was no evidence that study design, disease risk, or multifaceted intervention versus formula alone, impacted on study outcomes. However there were significant subgroup differences according to type of HF. There was evidence that pHF-whey and eHF-casein reduce risk of wheeze, but no such evidence for eHF-whey, with no statistical heterogeneity. Only one study had a low risk of overall bias and low risk of conflict of interest (Chan-Yeung), but in this multifaceted intervention study there was very low uptake of the pHF component of the intervention (8% of participants in the active intervention arm).

Figure 21 AnyHF vs CM for preventing wheeze at 0-4 years

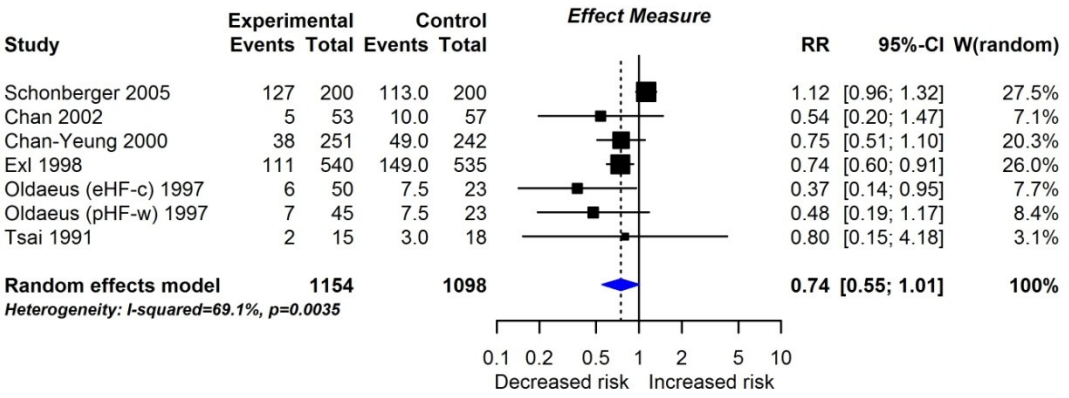


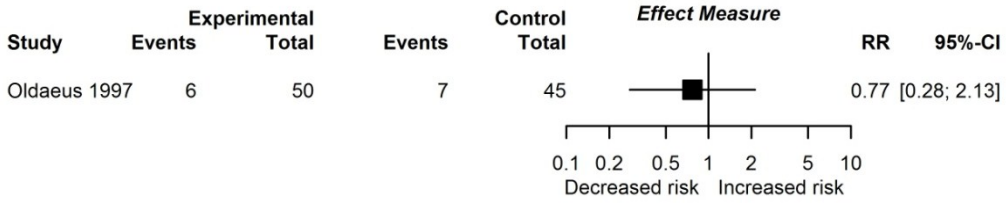
Table 4 Subgroup analysis of Any HF vs CM and risk of wheeze in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	1	0.74 [0.60-0.91]	-	0.89
Design – RCT	6	0.72 [0.47-1.08]	63.6	
Risk of disease – High	6	0.72 [0.47-1.08]	63.6	0.89
Risk of disease – Normal/Low	1	0.74 [0.60-0.91]	-	
HF type – eHF-casein	1	0.37 [0.14-0.95]	-	
HF type – eHF-whey	1	1.12 [0.96-1.32]	-	0.0003
HF type – pHF-whey	5	0.72 [0.60-0.86]	0	
Intervention protocol – Formula	5	0.70 [0.57-0.85]	0	0.18
Intervention protocol – Multifaceted	2	0.95 [0.63-1.44]	75.4	
Overall risk of bias – Low	1	0.75 [0.51-1.10]	-	0.92
Overall risk of bias – High/Unclear	6	0.73 [0.50-1.06]	72.6	
Conflict of interest bias – Low	1	0.75 [0.51-1.10]	-	0.92
Conflict of interest bias – High/Unclear	6	0.73[0.50-1.06]	72.6	

4.5. eHF vs pHF and risk of wheeze in children at age 0-4

One study reported eHF vs pHF and risk of wheeze in children aged 0-4, shown in Figure 22. There was no evidence of reduced risk of wheeze with wide confidence intervals due to small sample size.

Figure 22 eHF vs pHF for preventing wheeze at 0-4 years



4.6. eHF vs pHF and risk of wheeze in children at age 5-14

Schmitz used short term pHF compared with CM, and reported no significant difference between groups in wheeze prevalence in the first year, but did not give numerical data.

4.7. Short term use of HF and risk of wheeze at age 0-4

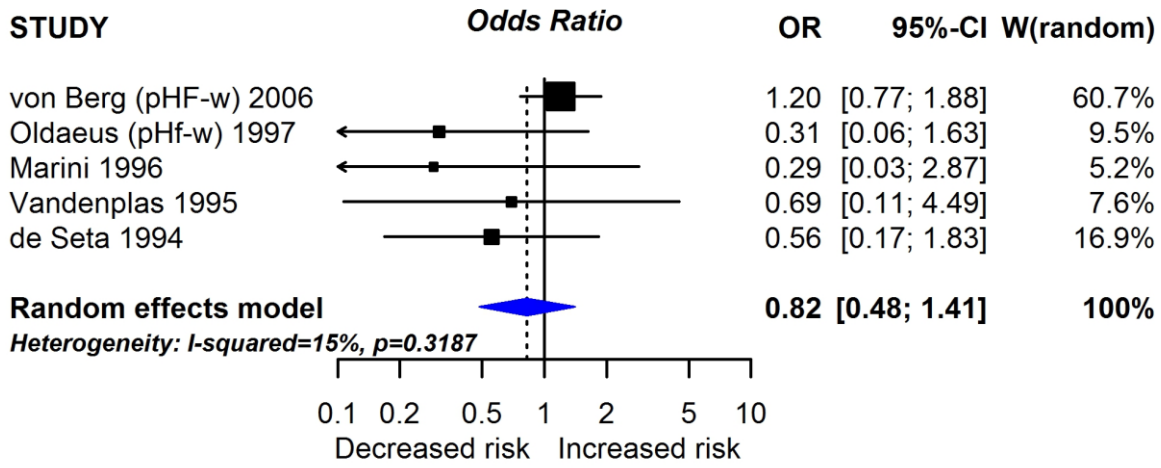
The study of Scalabrin found no significant difference between groups in doctor diagnosed wheeze at age 5 years. They assessed 64 children randomised to eHF-c (half randomised to eHF-c with a probiotic), and 37 randomised to pHF at this age, but did not report numerical data that could be included in meta-analysis.

4.8. pHF vs CM and risk of recurrent wheeze in children at age 0-4

Five studies reported pHF vs CM and risk of recurrent wheeze in children aged 0-4, shown in Figure 23. All studies were in children at high risk of allergic disease. The pooled data show no evidence of reduced risk of recurrent wheeze with low heterogenenity (I^2 = 15%).

The studies of von Berg, Marini and Vandenplas also reported recurrent wheeze at multiple other timepoints within the 0-4 year grouping, with similar findings to the most complete data from these studies, which are shown in Figure 23.

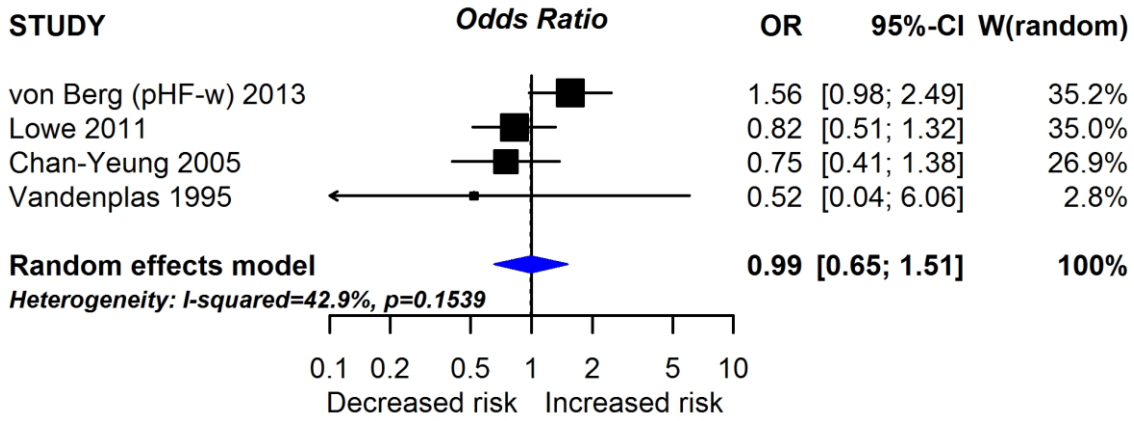
Figure 23 pHF vs CM for preventing recurrent wheeze at 0-4 years



4.9. pHF vs CM and risk of recurrent wheeze in children at age 5-14

Four studies reported pHF vs CM and risk of recurrent wheeze in children aged 5-14, shown in Figure 24. All studies were in children at high risk of allergic disease. The pooled data show no evidence of reduced recurrent wheeze with moderate statistical heterogenenity (I^2 = 43%). Von Berg reported related data in several publications, which all showed no evidence of association.

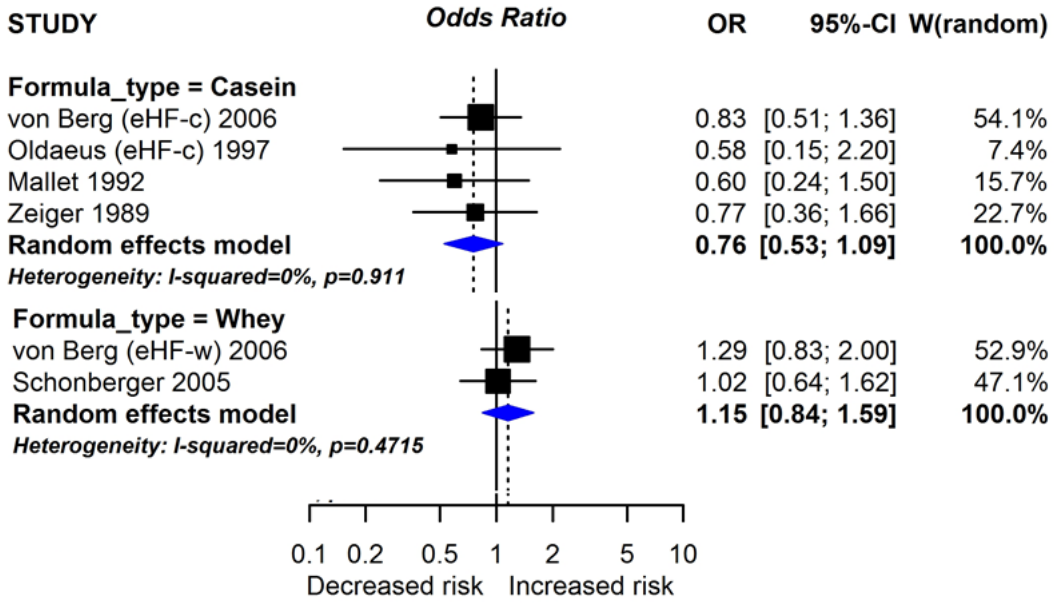
Figure 24 pHF vs CM for preventing recurrent wheeze at 5-14 years



4.10. eHF vs CM and risk of recurrent wheeze in children at age 0-4

Five studies (six interventions) reported eHF vs CM and risk of recurrent wheeze in children aged 0-4, shown in Figure 25. All studies were in children at high risk of allergic disease. The pooled data show no evidence of association for eHF-w or eHF-c, with no statistical heterogenenity (I^2 = 0%). The studies of von Berg, Schonberger, Mallet, and Zeiger all reported this outcome at other ages too, within the 0-4 age band, with similar findings. The study of Olderam measured recurrent wheeze as an outcome, but data were not reported for individual outcomes and only reported as total 'any allergic disease' with 15/32 in the CM group and 10/25 in the eHF group.

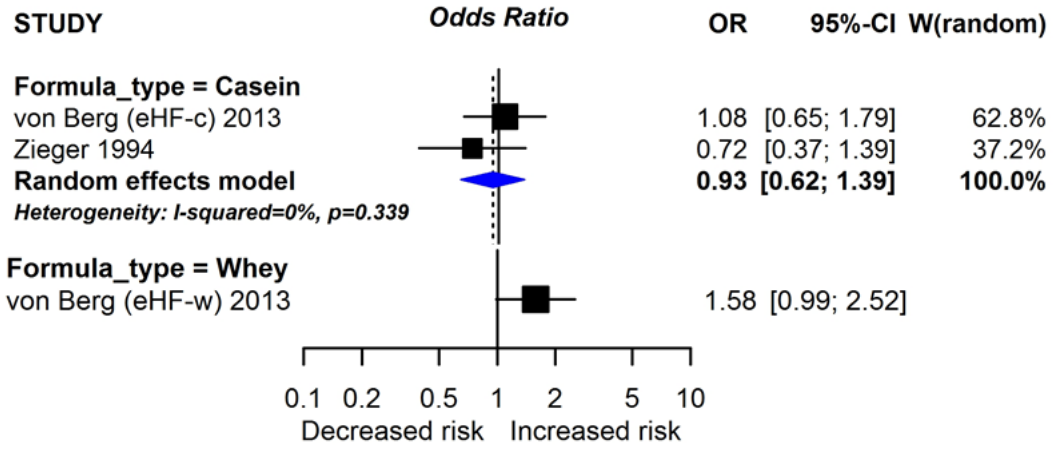
Figure 25 eHF vs CM for preventing recurrent wheeze at 0-4 years



4.11. eHF vs CM and risk of recurrent wheeze at age 5-14

Two studies (three interventions) reported eHF vs CM and risk of recurrent wheeze in children aged 5-14, shown in Figure 26. Both studies were in children at high risk of allergic disease. The pooled data show no evidence of reduced risk of recurrent wheeze, with no statistical heterogeneity. The studies of von Berg and Zeigler reported similar findings at other time points or using alternative measures of recurrent wheeze, within this age band.

Figure 26 eHF vs CM for preventing recurrent wheeze at 5-14 years



4.12. AnyHF vs CM and risk of recurrent wheeze at age 0-4

Eight studies reported AnyHF vs CM and risk of recurrent wheeze in children aged 0-4, shown in Figure 27. All studies were in children at high risk of allergic disease. The pooled data shows no evidence of reduced risk of recurrent wheeze with no statistical heterogenenity (I^2 = 0%). A Funnel plot to explore publication bias is shown in Figure 28 and shows evidence of publication bias (P=0.021), suggesting the possibility of small negative unpublished trials.

Subgroup analyses are shown in Table 5. There was no evidence that multifaceted intervention versus formula alone or hydrolysed formula type impacted on study outcomes. No study had a low risk of bias or low risk of conflict of interest.

Figure 27 AnyHF vs CM for preventing recurrent wheeze at 0-4 years

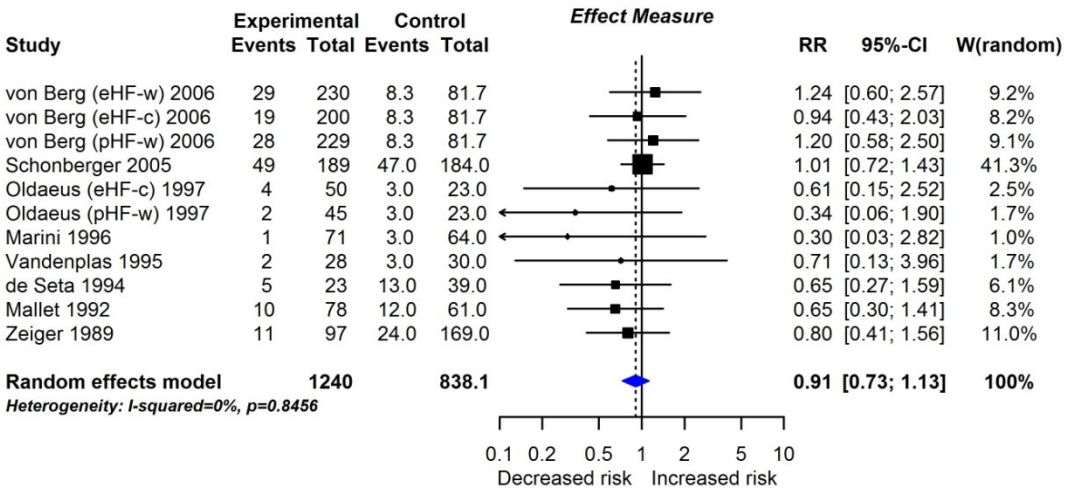
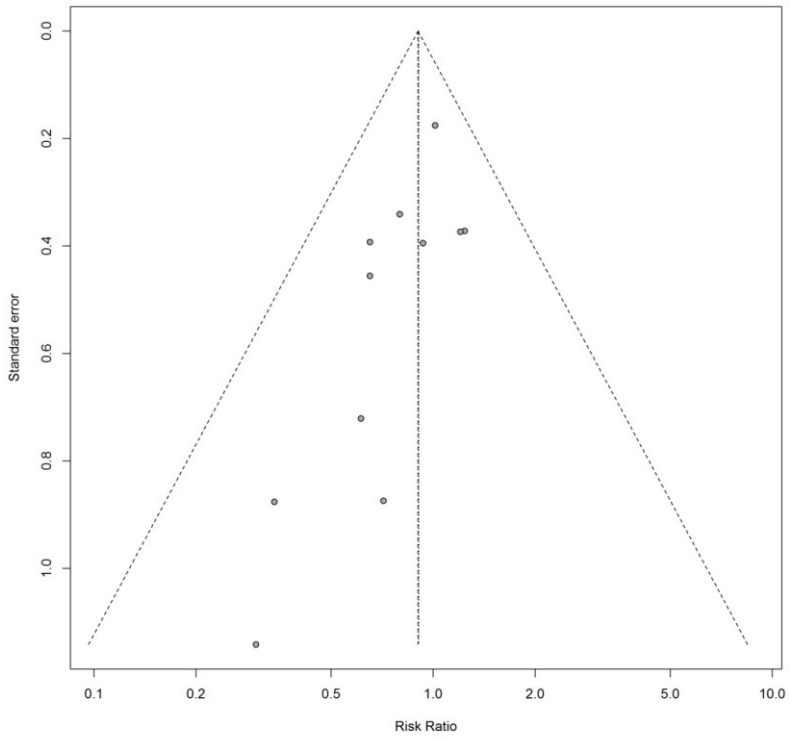


Figure 28 Funnel plot for AnyHF vs CM and risk of recurrent wheeze at age 0-4



Egger's Test p-value = 0.021

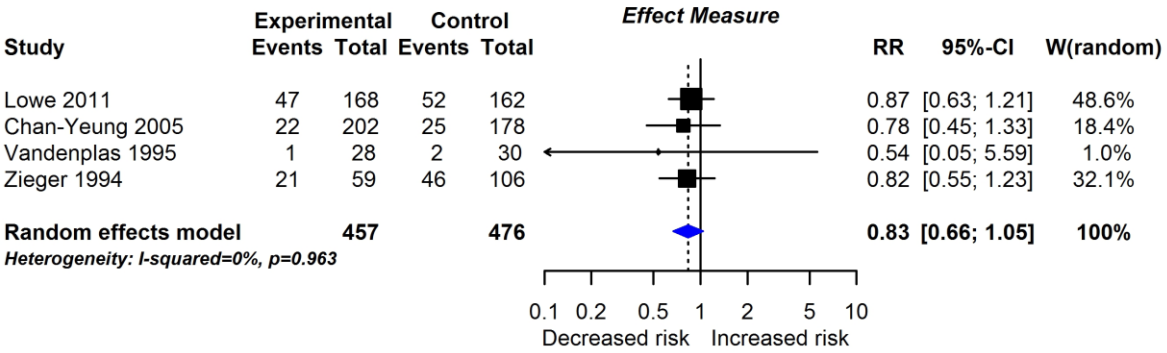
Table 5 Subgroup analysis of Any HF vs CM and recurrent wheeze risk in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	0	-	-	-
Design – RCT	11	0.90 [0.72-1.12]	0	
Risk of disease – High	11	0.90 [0.72-1.12]	0	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF-casein	4	0.77 [0.51-1.16]	0	
HF type – eHF-whey	2	1.05 [0.77-1.44]	0	0.31
HF type – pHF-whey	5	0.68 [0.36-1.27]	25.5	
Intervention protocol – Formula	9	0.83 [0.60-1.14]	0	0.50
Intervention protocol – Multifaceted	2	0.97 [0.71-1.31]	0	
Overall risk of bias – Low	0	-	-	-
Overall risk of bias – High/Unclear	11	0.90 [0.72-1.12]	0	
Conflict of interest bias – Low	0	-	-	-
Conflict of interest bias – High/Unclear	11	0.90 [0.72-1.12]	0	
	70			

4.13. Any HF vs CM and risk of recurrent wheeze at age 5-14

Five studies reported AnyHF vs CM and risk of recurrent wheeze in children aged 5-14. All studies were in children at high risk of allergic disease. Four studies could be included in meta-analysis, shown in Figure 29. The pooled data shows no evidence of reduced risk of recurrent wheeze with no statistical heterogenenity ($I^2 = 0\%$). All studies had high or unclear risk of bias and risk of conflict of interest. The GINI study (von Berg) reported GEE data at age 10 for this outcome, which could not be included in this meta-analysis. There was no reduction in recurrent wheeze with pHF (OR 1.56 95% CI 0.97, 2.49), with eHF-w (OR 1.58 95% CI 0.99, 2.52) or with eHF-c (OR 1.08 95% CI 0.66, 1.79) compared with standard cow's milk formula.

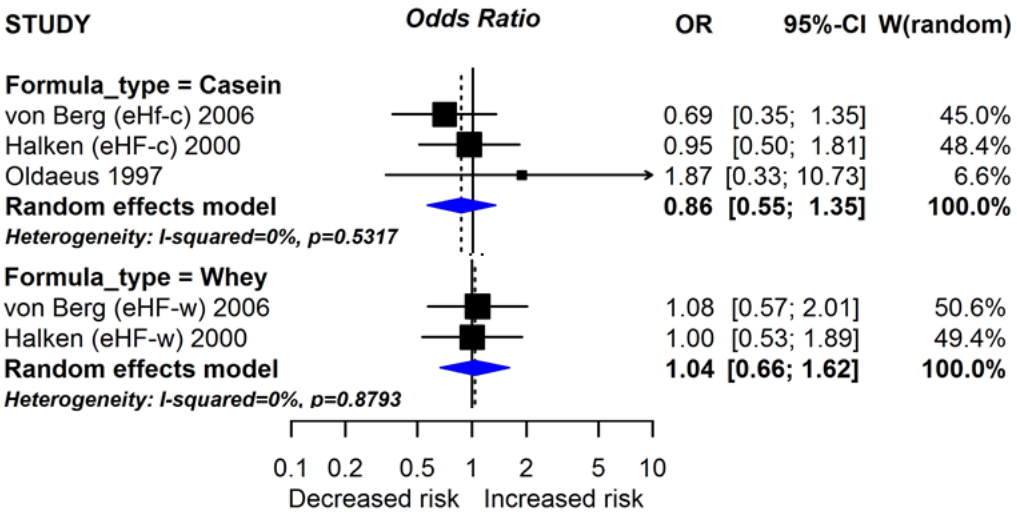
Figure 29 AnyHF vs CM for preventing recurrent wheeze at 5-14 years



4.14. eHF vs pHF and risk of recurrent wheeze at age 0-4

Four studies (five interventions) reported eHF vs pHF and risk of recurrent wheeze in children aged 0-4, shown in Figure 30. The pooled data show no evidence of reduced risk of recurrent wheeze with eHF-w or eHF-c, and with no heterogenenity ($I^2 = 0\%$).

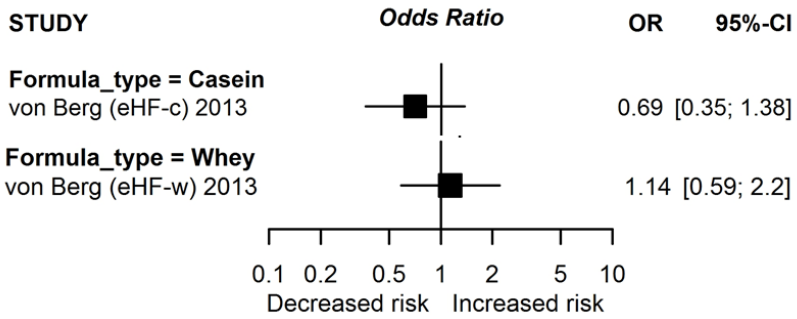
Figure 30 eHF vs pHF for preventing recurrent wheeze at 0-4 years



4.15. eHF vs pHF and risk of recurrent wheeze at age 5-14

One study (two interventions) reported numerical data for eHF vs pHF and risk of recurrent wheeze in children aged 0-4, shown in Figure 31. The pooled data show no evidence of reduced risk of recurrent wheeze with eHF-w or eHF-c. The study of Scalabrin also found no significant difference between groups in doctor diagnosed asthma at age 5 years. They assessed 64 children randomised to eHF-c (half randomised to eHF-c with a probiotic), and 37 randomised to pHF at this age, but did not report numerical data that could be included in meta-analysis.

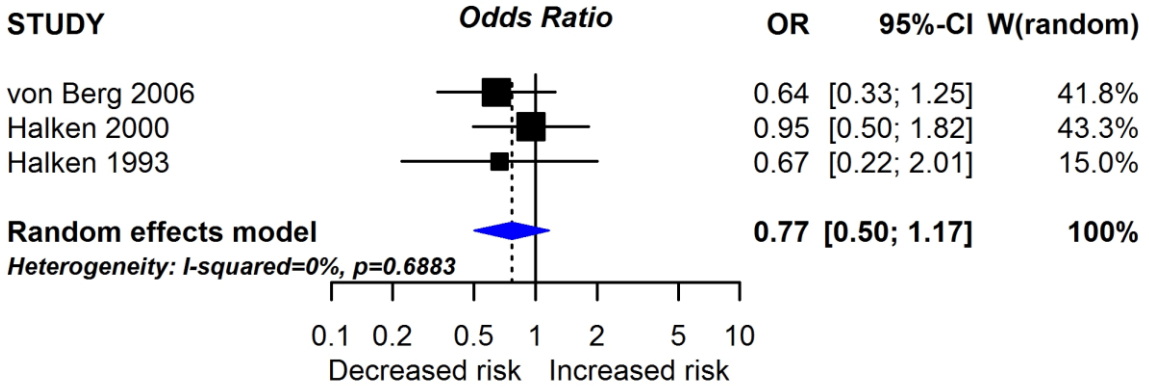
Figure 31 eHF vs pHF for preventing recurrent wheeze at 5-14 years



4.16. eHF-c vs eHF-w and risk of recurrent wheeze at age 0-4

Three studies reported eHF-c vs eHF-w and risk of recurrent wheeze in children aged 0-4, shown in Figure 32. The pooled data show no reduced risk of recurrent wheeze with eHF-c. There is no statistical heterogenenity ($I^2 = 0\%$).

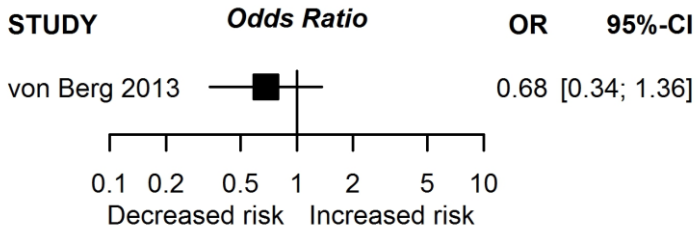
Figure 32 eHF-c vs eHF-w for preventing recurrent wheeze at 0-4 years



4.17. eHF-c vs eHF-w and risk of recurrent wheeze at age 5-14

One study reported eHF-c vs eHF-w and risk of recurrent wheeze in children aged 5-14, shown in Figure 33. There is no evidence that eHF-c reduces risk of recurrent wheeze in children aged 5-14.

Figure 33 eHF-c vs eHF-w for preventing recurrent wheeze at 5-14 years



4.18. Short term use of HF and risk of recurrent wheeze at age 0-4

One study reported eHF vs CM or HM and risk of recurrent wheeze in children aged 0-4, shown in Figure 34 (eHF vs CM) and 35 (eHF vs HM). There is no evidence of reduced risk of recurrent wheeze with use of eHF for a short period of time.

Figure 34 eHF vs CM_Short for preventing recurrent wheeze at 0-4 years

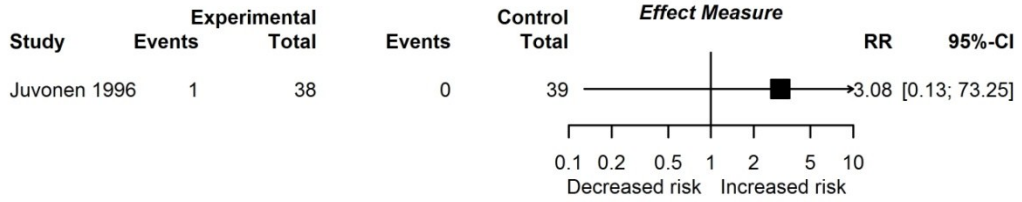
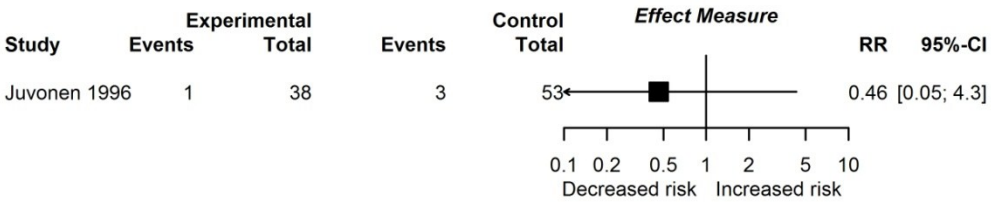


Figure 35 eHF vs HM_Short for preventing recurrent wheeze at 0-4 years



4.19. pHF vs CM and lung function at age 5-14

One study reported pHF vs CM and measures of respiratory function at age 5-14. There was no evidence of reduced risk of bronchial hyper-responsiveness (BHR; Figure 36) or increased forced expiratory volume in 1second (FEV1; Figure 37).

Figure 36 pHF vs CM and BHR (Metacholine PC20<7.8mg/ml) at 5-14 years

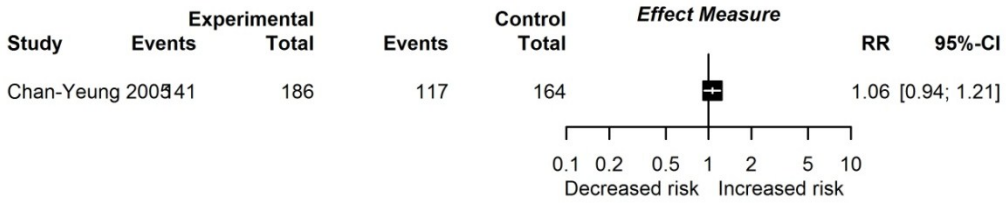
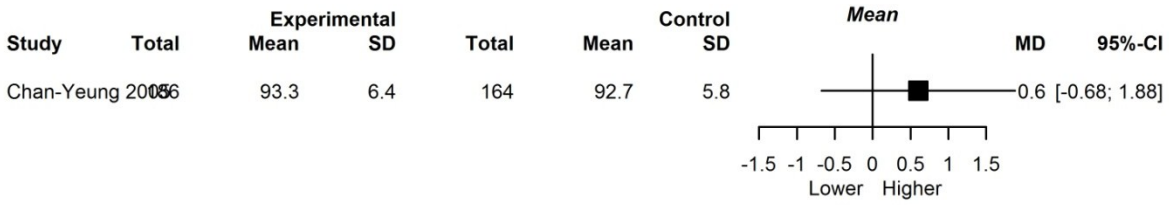


Figure 37 pHF vs CM and FEV1 (% predicted) at 5-14 years



4.20. Conclusions

These data were largely derived from studies with high or unclear risk of bias, and high or unclear risk of conflict of interest. Almost all studies were undertaken in children at high risk due to family history of allergic disease, so the data may only be relevant to this population.

There was some evidence that the use of pHF in place of standard formula reduces the risk of wheeze in children aged 0-4 or aged 5-14. The analysis at age 0-4 was dominated by the study of 'normal risk' children by Exl et al, which we judged to have both high overall risk of bias (qRCT) and high risk of conflict of interest due to industry involvement (some authors and the correspondence address were based at Nestlé, the formula manufacturer). The analysis at age 5-14 for pHF vs CM included one study only, which was a multifaceted intervention trial in which relatively few participants used the pHF formula (8% in the intervention arm). There was no evidence that eHF reduces risk of wheeze.

In analyses of recurrent wheeze, which included a similar number of participants and studies overall as analyses of single wheeze, there was low statistical heterogeneity in almost all analyses. Here there was no evidence that either pHF or eHF reduce risk of recurrent wheeze, compared with unhydrolysed formula. We nevertheless found evidence of Funnel plot asymmetry in reports of HF and recurrent wheeze, which may reflect publication bias or small study effects.

Separate analyses of eHF vs pHF (wheeze, recurrent wheeze) and eHF-c vs eHF-w (recurrent wheeze only) did not show evidence of differential effects, although these analyses were limited by small numbers of studies and participants contributing data.

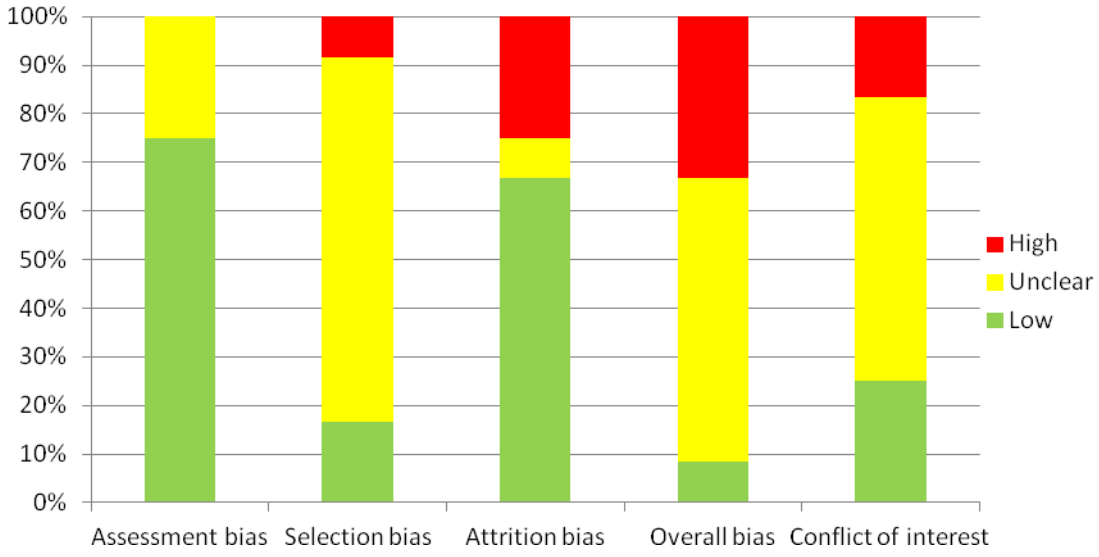
We found no evidence that short term feeding with eHF in the first days of life has any advantage over either human milk or unhydrolysed formula milk, but these analyses were essentially inconclusive due to very small sample size.

Given the overall risk of bias and risk of conflict of interest in relevant studies, and the finding of possible publication bias, at least for reporting of HF and recurrent wheeze - we conclude that there is no evidence to support an association between infant feeding with a partially or extensively hydrolysed formula and reduced wheezing risk.

5. Hydrolysed formula and risk of allergic rhinoconjunctivitis (AR)

Twelve intervention studies investigated the effect of hydrolysed formula on risk of AR or AC, in over 2500 participants. One third of studies were considered to be at high risk of bias, mainly due to high attrition bias (>30% of randomised participants not analysed for the outcome). Three quarters of studies had high or unclear risk of conflict of interest, due to possible or probable industry involvement in the study design, analysis or publication (Figure 38).

Figure 38 Risk of bias in intervention studies of HF and AR



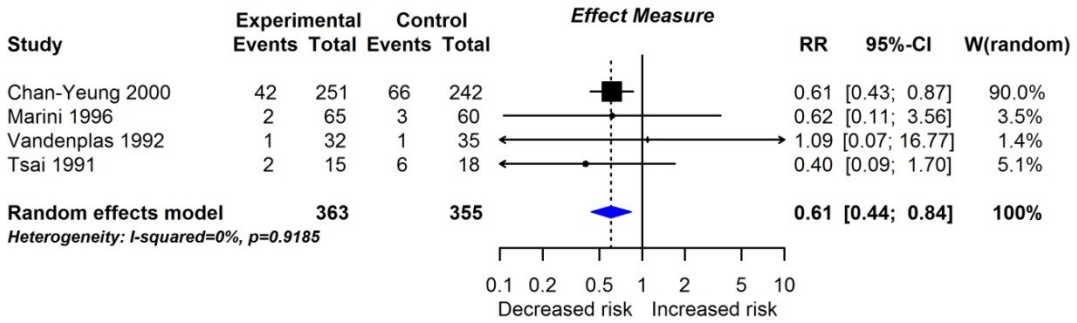
5.1. pHF vs CM and risk of AR age 0-4 years

Four studies reported pHF vs CM and risk of AR in children aged 0-4, shown in Figure 39. All studies were restricted to children at high risk of allergic outcomes. The pooled data show reduced risk of AR with pHF, with no statistical heterogenenity ($I^2 = 0\%$). The analysis was dominated by the multifaceted intervention study of Chan-Yeung, where uptake of the pHF intervention was low (8% of partipants randomised to the active intervention).

Data not included in meta-analysis

Vandenplas also reported this outcome at other ages within the 0-4 band, with similar findings. Two further studies could not be included in meta-analysis. Oldaeus reported no cases of AR in either intervention (n=45) or control (n=46) group at 18 months. Willems (n=67) recorded AR in their trial, but did not report data for this outcome.

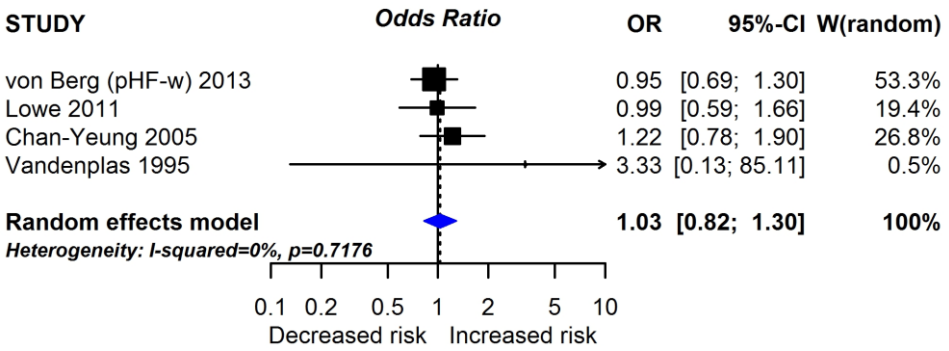
Figure 39 pHF vs CM for preventing AR at 0-4 years



5.2. pHF vs CM and risk of AR at 5-14 years

Four studies reported pHF vs CM and risk of AR in children aged 5-14, shown in Figure 40. The pooled data show no evidence of reduced risk of AR with no statistical heterogenenity (I^2 = 0%). Von Berg also reported AR at other ages within the 5-14 band, with similar negative findings.

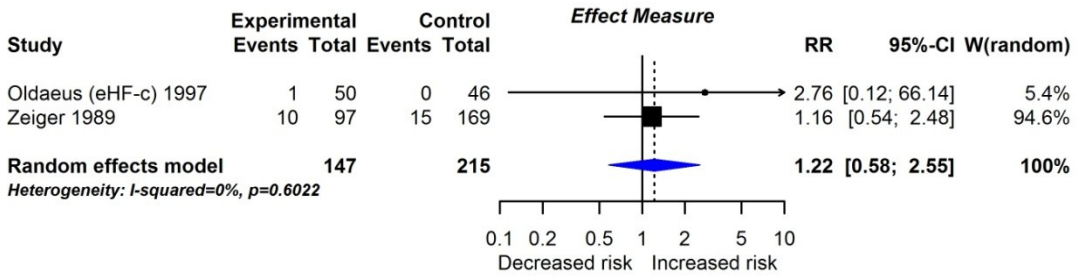
Figure 40 pHF vs CM for preventing AR at 5-14 years



5.3. eHF vs CM and risk of AR at age 0-4

Two studies reported eHF vs CM and risk of AR in children aged 0-4, shown in Figure 41. The pooled data show no evidence of reduced risk of AR, with no heterogenenity (I^2 = 0%). The study of Zeiger reported similar findings at age 1 (shown in Figure 41) and age 7. The study of Odelram (n=57) recorded this outcome, but did not report any data for AR specifically – just that there was no difference for 'any allergic disease'.

Figure 41 eHF vs CM for preventing AR at 0-4 years



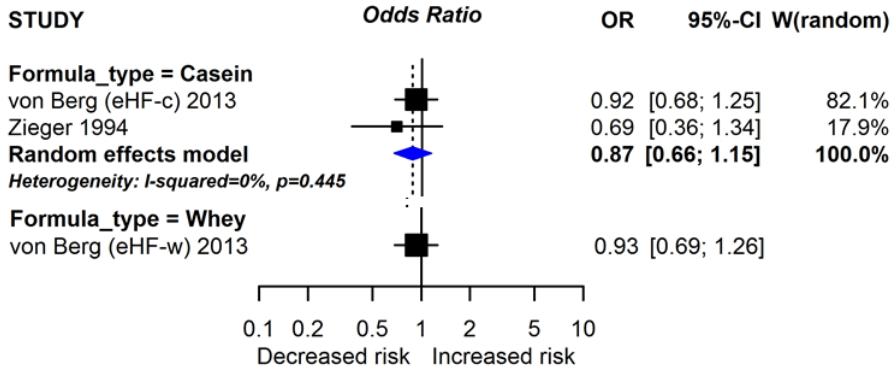
5.4. eHF vs CM and risk of AR at age 5-14

Two studies with 3 comparisons reported eHF vs CM and risk of AR in children aged 5-14, shown in Figure 42. There is no evidence that use of eHF reduces risk of AR, with no statistical heterogenenity ($I^2 = 0\%$).

Data not included in meta-analysis

Von Berg reported this outcome at other ages within the 5-14 band, with similar negative findings; Zeiger also reported this outcome as period prevalence, with similar negative findings to those shown in Figure 42.

Figure 42 eHF vs CM for preventing AR at 5-14 years



5.5. AnyHF vs CM and risk of AR at age 0-4

Overall 6 studies reported AnyHF vs CM and risk of AR in children aged 0-4, shown in Figure 43. There is evidence that the use of any hydrolysed formula reduces the risk of AR and with low heterogeneity (I^2 = 0%). Subgroup analyses are shown in Table 6. There was weak evidence that pHF-whey may be more effective than eHF-casein for preventing AR.

A single study with low overall risk of bias, low risk of conflict of interest and inclusion of environmental control measures including cigarette smoking avoidance with the intervention, dominated the analysis of pHF (Chan-Yeung). This study found a protective effect of pHF when used as part of a multifaceted intervention, on AR at 0-4 but not at 5-14 however uptake of pHF within the intervention arm was low (8%).

Figure 43 AnyHF vs CM for preventing AR at 0-4 years

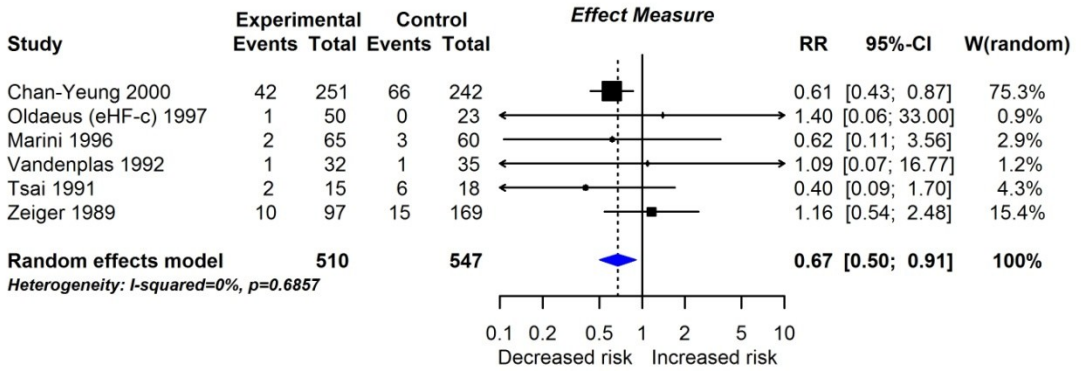


Table 6 Subgroup analysis of any HF vs CM and AR risk in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	0	-	-	-
Design – RCT	6	0.65 [0.45-0.94]	8.3	
Risk of disease – High	6	0.65 [0.45-0.94]	8.3	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF-Casein	2	1.17 [0.56-2.46]	0	0.083
HF type – pHF-Whey	4	0.57 [0.42-0.80]	0	
Intervention protocol – Formula	4	0.39 [0.15-0.98]	0	0.22
Intervention protocol – Multifaceted	2	0.77 [0.42-1.40]	55.6	
Overall risk of bias – Low	1	0.61 [0.43-0.87]	-	0.87
Overall risk of bias – High/Unclear	5	0.66 [0.31-1.42]	23.1	
Conflict of interest bias – Low	1	0.61 [0.43-0.87]	-	0.87
Conflict of interest bias – High/Unclear	5	0.66 [0.31-1.42]	23.1	

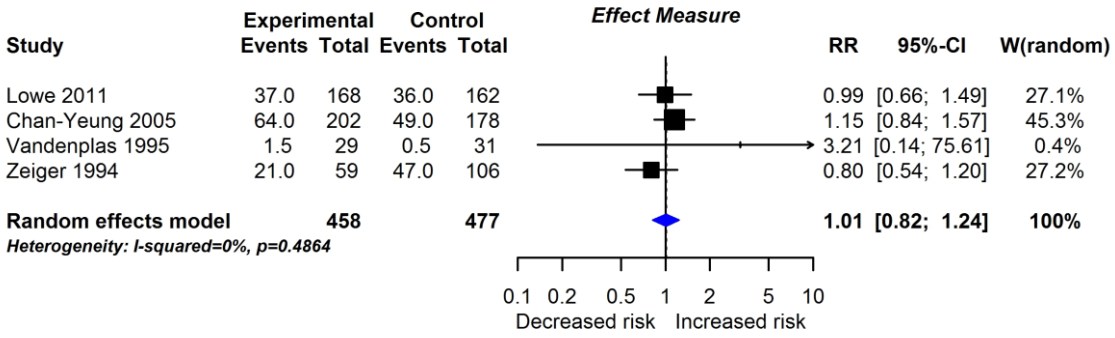
5.6. AnyHF vs CM and risk of AR at age 5-14

Overall 5 studies with 7 interventions reported AnyHF vs CM and risk of AR in children aged 5-14. Four studies could be included in meta-analysis together, shown in Figure 44. There is no evidence that the use of any hydrolysed formula reduces the risk of AR at this age, with no heterogeneity ($I^2 = 0\%$).

Data not included in meta-analysis

The GINI study (von Berg) reported GEE data at age 10 for this outcome, which could not be included in this meta-analysis. There was no reduction in recurrent wheeze with pHF (OR 0.95 95% CI 0.69, 1.30), with eHF-w (OR 0.93 95% CI 0.69, 1.26) or with eHF-c (OR 0.92 95% CI 0.67, 1.25) compared with standard cow's milk formula.

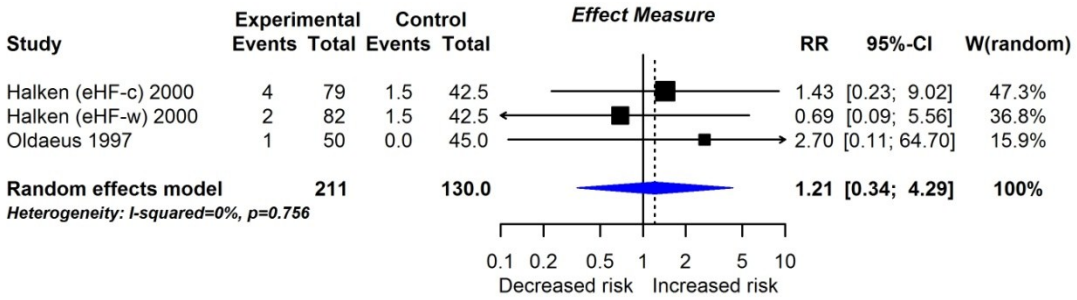
Figure 44 AnyHF vs CM for preventing AR at 5-14 years



5.7. eHF vs pHF and risk of AR at age 0-4

Two studies with 3 interventions reported eHF vs pHF and risk of AR in children aged 0-4, shown in Figure 45. The data show no evidence of reduced risk of AR with the use of eHF, with no heterogenenity ($I^2 = 0\%$).

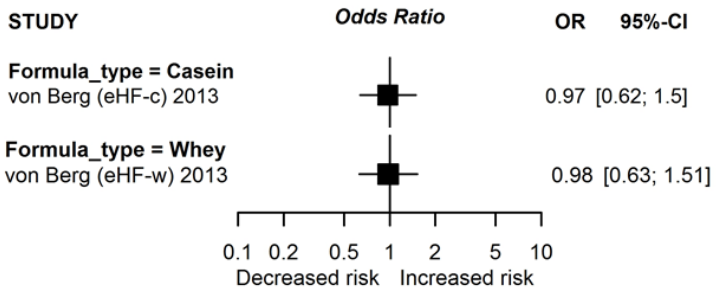
Figure 45 eHF vs pHF for preventing AR at 0-4 years



5.8. eHF vs pHF and risk of AR at age 5-14

One study with 2 interventions reported eHF vs pHF and risk of AR in children aged 5-14, shown in Figure 46. There was no evidence that the use of eHF-w or eHF-c reduces AR risk compared with pHF. A second study (Scalabrin) also found no significant difference between groups in doctor diagnosed AR at age 5 years. They assessed 64 children randomised to eHF-c (half randomised to eHF-c with a probiotic), and 37 randomised to pHF at this age, but did not report numerical data that could be included in meta-analysis.

Figure 46 eHF vs pHF for preventing AR at 5-14 years



5.9. eHF-c vs eHF-w and risk of AR

One study reported eHF-c vs eHF-w and risk of AR in children aged 0-4, shown in Figure 47; and one at age 5-14 (Figure 48). There is no evidence that the use of eHF-c reduces risk of AR, compared with eHF-w.

Figure 47 eHF-c vs eHF-w for preventing AR at 0-4 years

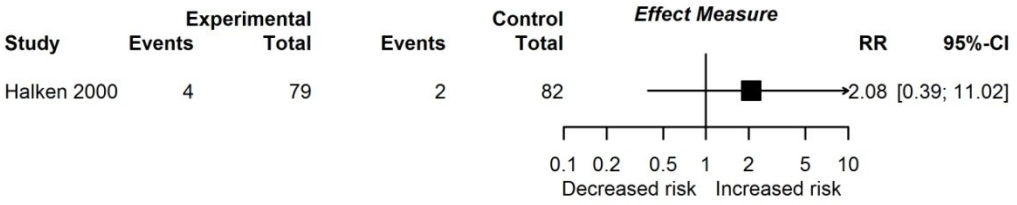
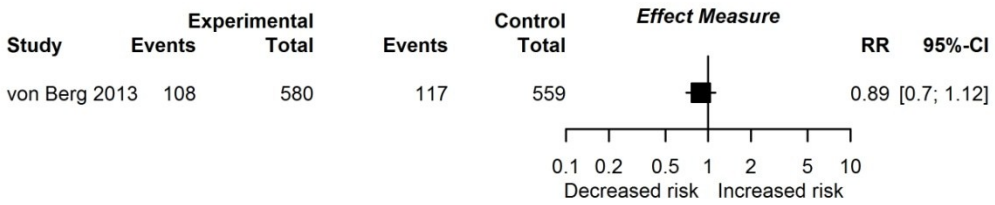


Figure 48 eHF-c vs eHF-w for preventing AR at 5-14 years



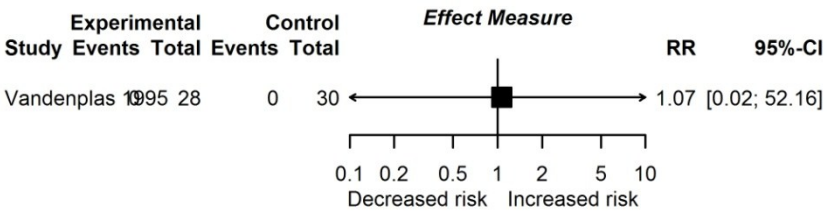
5.10. Short term use of HF and risk of AR at age 0-4

Schmitz used short term pHF compared with CM, and reported no significant difference between groups in AR prevalence in the first year, but did not give numerical data.

5.11. pHF vs CM and risk of Allergic Conjunctivitis at age 0-4

One study reported pHF vs CM and risk of AC in children aged 0-4, shown in Figure 49. There is no evidence that the use of pHF reduces risk of AC.

Figure 49 pHF vs CM for preventing AC at 0-4 years



5.12. Conclusions

These data were largely derived from studies with high or unclear risk of bias, and high or unclear risk of conflict of interest. All studies were undertaken in children at high risk of allergic outcomes.

We found some evidence that the use of pHF compared with standard non-hydrolysed cow's milk formula reduces AR risk at age 0-4, but not at age 5-14. There is no evidence that the use of eHF is protective against AR. Direct comparison found no evidence that eHF reduces AR compared with pHF, or eHF-c compared with eHF-w, in either age group.

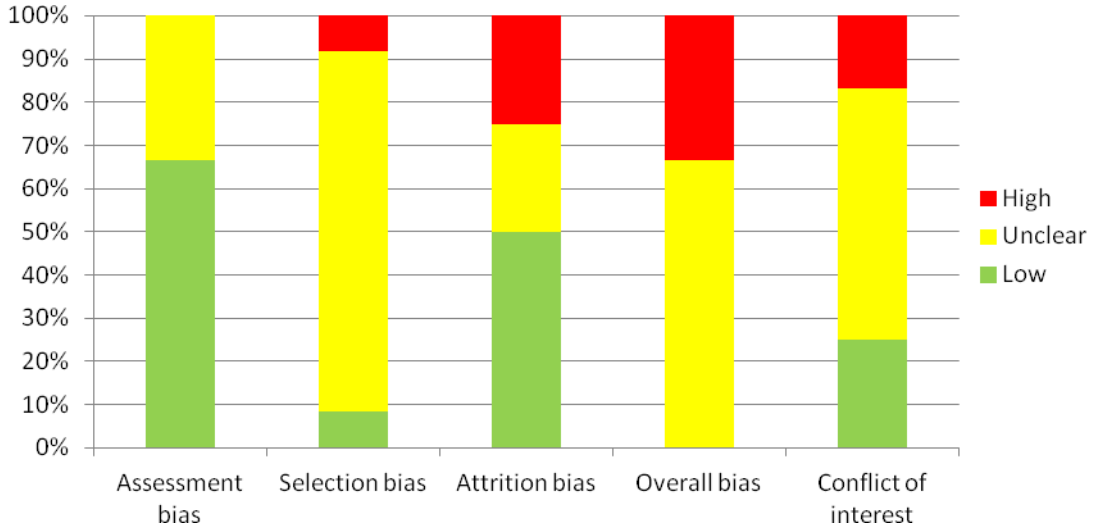
The positive finding for pHF at age 0-4 was found in meta-analysis of ~700 participants and was dominated by positive findings in one multifaceted intervention trial (Chan-Yeung; CAPPS study). Although the CAPPS study was judged to be at low overall risk of bias, and low risk of conflict of interest, the uptake of pHF was low in this study and the intervention included environmental control measures and avoidance of cigarette smoke which may be relevant to the positive finding. A further 150 participants were randomised to pHF vs CM in other studies where AR was recorded as an outcome, and here findings were either negative or not reported, but could not be included in the meta-analysis. Analyses at age 5-14, where AR is more reliably identified, included larger numbers of participants (~1800 for pHF vs CM) and showed no evidence of an effect, including no evidence in the CAPPS study. We were unable to formally assess for publication bias due to the small number of studies included in analyses, but note the publication bias identified for other outcomes in this hydrolysed formula review.

In conclusion we found some evidence that a multifaceted intervention trial incorporating environmental control measures as well as pHF may reduce risk of AR at age 0-4 (but not age 5-14). We did not find any evidence that pHF or eHF alone protect against AR, compared with standard cow's milk formula.

6. Hydrolysed formula and risk of food allergy (FA)

Thirteen intervention studies investigated the effect of hydrolysed formula on risk of FA, in over 9500 participants. One third of studies were considered to be at high risk of bias, mainly due to high attrition bias (>30% of randomised participants not analysed for the outcome). Three quarters of studies had high or unclear risk of conflict of interest, due to possible or probable industry involvement in the study design, analysis or publication (Figure 50).

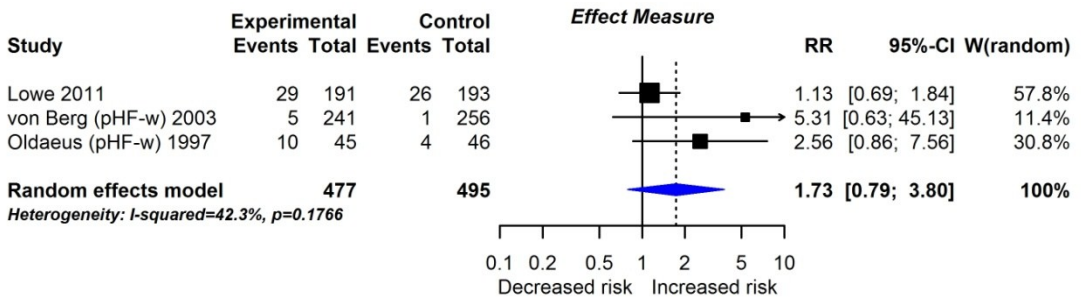
Figure 50 Risk of bias in intervention studies of HF and food allergy



6.1. pHF vs CM and risk of food allergy (any) at age 0-4

Three studies reported pHF vs CM and risk of food allergy (any) in children aged 0-4, shown in Figure 51. The pooled data show no evidence of an effect, with moderate heterogenenity ($I^2 = 42.3\%$).

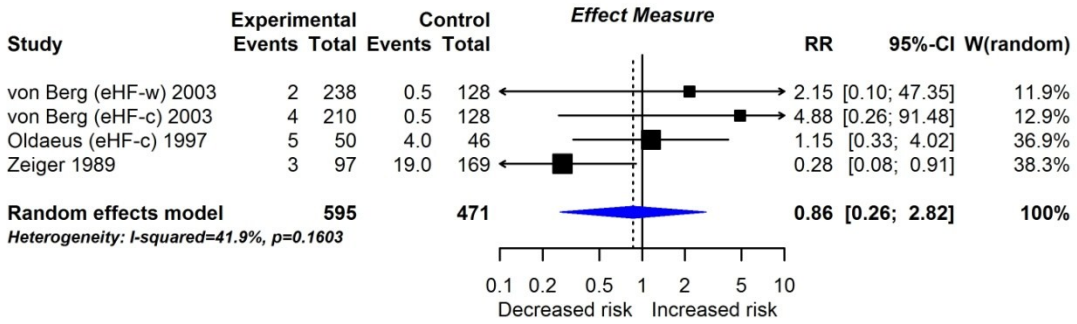
Figure 51 pHF vs CM for preventing food allergy (any) at age 0-4



6.2. HF vs CM and risk of food allergy (any) at age 0-4

Two studies reported eHF vs CM and risk of eczema in children aged 0-4, shown in Figure 52. The pooled data show no evidence of reduced risk of food allergy (any) with moderate heterogeneity (I^2 = 41.9%). The study of Zeiger also reported this outcome at age 4, where there was no significant difference seen.

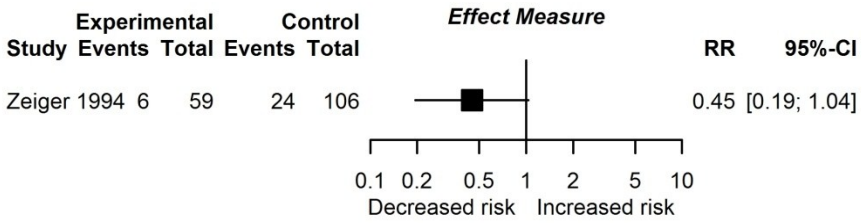
Figure 52 eHF vs CM for preventing food allergy (any) at age 0-4



6.3. eHF vs CM and risk of food allergy (any) at age 5-14

One study reported eHF vs CM and risk of food allergy (any) in children aged 5-14, shown in Figure 53. There was reduced risk of any food allergy for children ages 5-14 in the eHF group, but this did not reach statistical significance. The same study also reported data for this outcome reported as period prevalence rather than cumulative incidence, where they found no significant difference between treatment groups.

Figure 53 eHF vs CM for preventing food allergy (any) at 5-14 years



6.4. Any HF vs CM and risk of food allergy (any) at age 0-4

In total 4 studies with 7 interventions reported AnyHF vs CM and risk of any food allergy in children aged 0-4, shown in Figure 54. There is no evidence that the use of any hydrolysed formula reduces the risk of FA to any food, with moderate statistical heterogenenity (I^2 = 26.3%).

Subgroup analyses are shown in Table 7. There was no evidence that type of hydrolysed formula type impacted on study outcomes and no study had a low risk of overall bias or low risk of conflict of interest. The single trial of a multifaceted intervention (Zeiger 1989) showed a significantly more positive effect than the other trials. In the intervention arm of the study of Zeiger, mother and infant avoided common allergenic foods during the pre and postnatal periods, in addition to the use of eHF.

Figure 54 AnyHF vs CM for preventing food allergy (any) at age 0-4

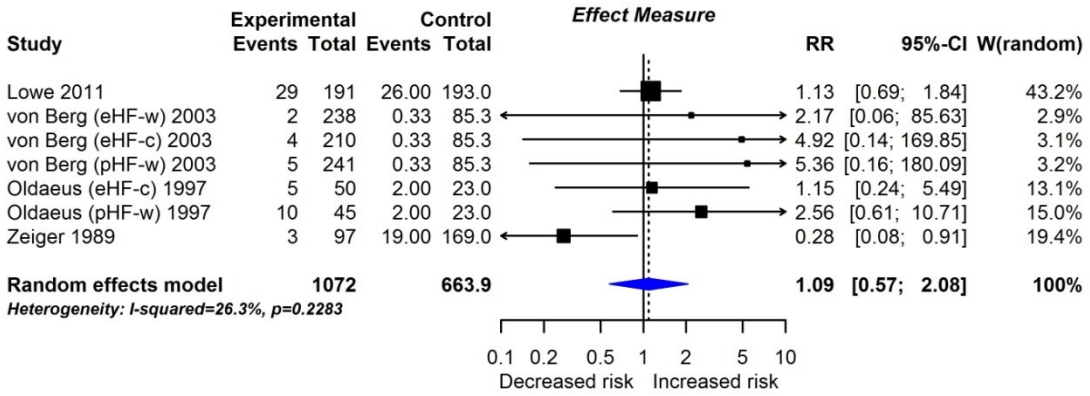


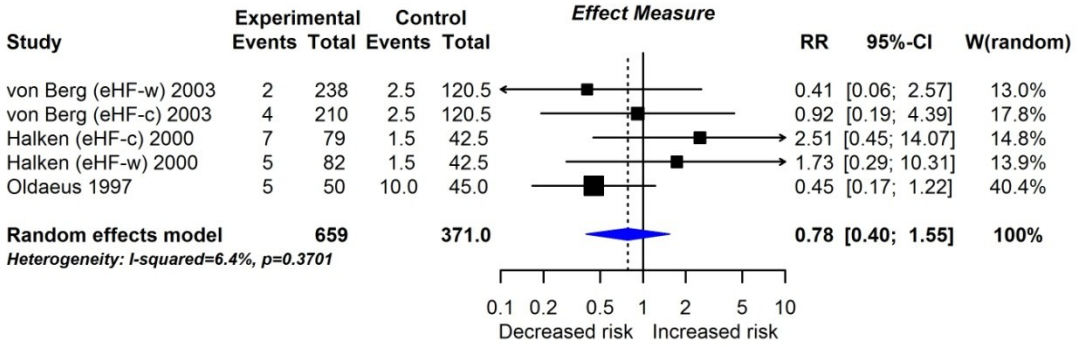
Table 7 Subgroup analysis of Any HF vs CM and food allergy (any) risk in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	0	-	-	-
Design – RCT	7	1.09 [0.57-2.08]	26.3	
Risk of disease – High	7	1.09 [0.57-2.08]	26.3	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF-Casein	3	0.69 [0.17-2.78]	44.8	
HF type – eHF-Whey	1	2.17 [0.06-85.63]	-	0.69
HF type – pHF-whey	3	1.26 [0.80-1.99]	0	
Intervention protocol – Formula	6	1.29 [0.83-1.99]	0	0.017
Intervention protocol – Multifaceted	1	0.28 [0.08-0.91]	-	
Risk of bias – Low	0	-	-	-
Risk of bias – High/Unclear	7	1.09 [0.57-2.08]	26.3	
Conflict of interest bias – Low	0	-	-	-
Conflict of interest bias – High/Unclear	7	1.09 [0.57-2.08]	26.3	

6.5. eHF vs pHF and risk of food allergy (any) at age 0-4 years

Three studies reported eHF vs pHF and risk of any food allergy in children aged 0-4, shown in Figure 55. There is no evidence that the use eHF reduces the risk of any food allergy compared with pHF, with low heterogeneity ($I^2 = 6.4\%$).

Figure 55 eHF vs pHF for preventing food allergy (any) at age 0-4



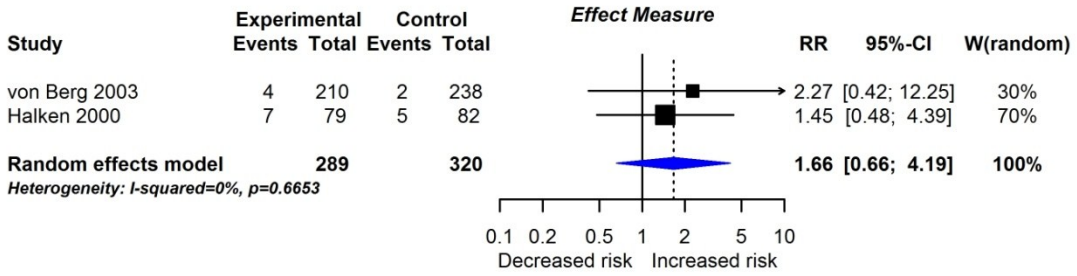
Data not included in meta-analysis

The study of Scalabrin found no significant difference between groups in doctor diagnosed food allergy at age 5 years. They assessed 64 children randomised to eHF-c (half randomised to eHF-c with a probiotic), and 37 randomised to pHF at this age, but did not report numerical data that could be included in meta-analysis.

6.6. eHF-c vs eHF-w and risk of food allergy (any) in children at age 0-4

Two studies reported eHF-c vs eHF-w and risk of any food allergy in children aged 0-4, shown in Figure 56. The pooled data show no evidence of differential risk of any food allergy, with low heterogenenity ($I^2 = 0\%$).

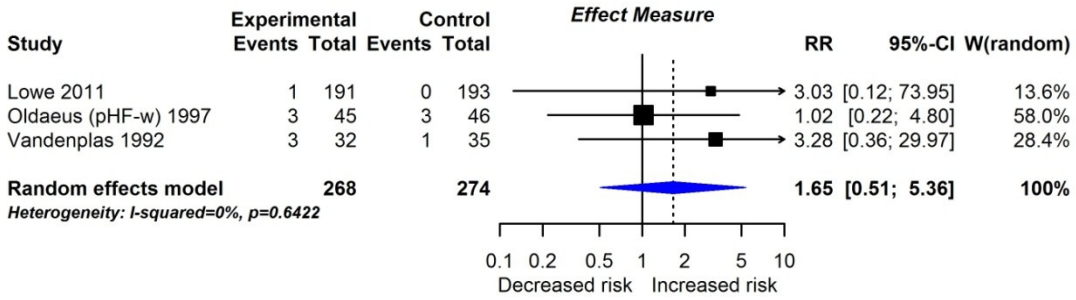
Figure 56 eHF-c vs eHF-w for preventing food allergy (any) at 0-4 years



6.7. pHF vs CM and risk of cow's milk allergy (CMA) at age 0-4

Three studies reported pHF vs CM and risk of CMA in children aged 0-4, shown in Figure 57. The pooled data show no evidence of reduced risk of CMA with pHF, with no heterogenenity ($I^2 = 0\%$).

Figure 57 pHF vs CM for preventing CMA at age 0-4



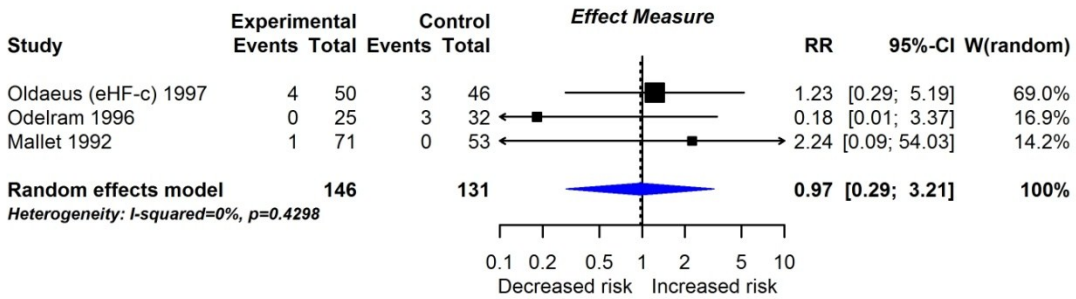
6.8. eHF vs CM and risk of CMA at age 0-4

Three studies reported eHF vs CM and risk of CMA in children aged 0-4, shown in Figure 58. The pooled data show no evidence of reduced risk of CMA with eHF with no heterogenenity ($I^2 = 0\%$).

Data not included in meta-analysis

The study of Vaarala also reported data on this outcome at 6 months – here it was unclear whether anyone in the eHF group developed CMA, whilst 1 child in control group did.

Figure 58 eHF vs CM for preventing CMA at age 0-4



6.9. Any HF vs CM and risk of CMA at age 0-4

In total 5 studies with 6 interventions reported AnyHF vs CM and risk of CMA in children aged 0-4, shown in Figure 59. There is no evidence that the use of any hydrolysed formula in children ages 0-4 reduces risk of CMA, with no heterogenenity ($I^2 = 0\%$).

Subgroup analyses are shown in Table 8. There was no evidence that type of hydrolysed formula or risk of conflict of interest of the researchers impacted on study outcomes.

Figure 59 AnyHF vs CM for preventing CMA at age 0-4

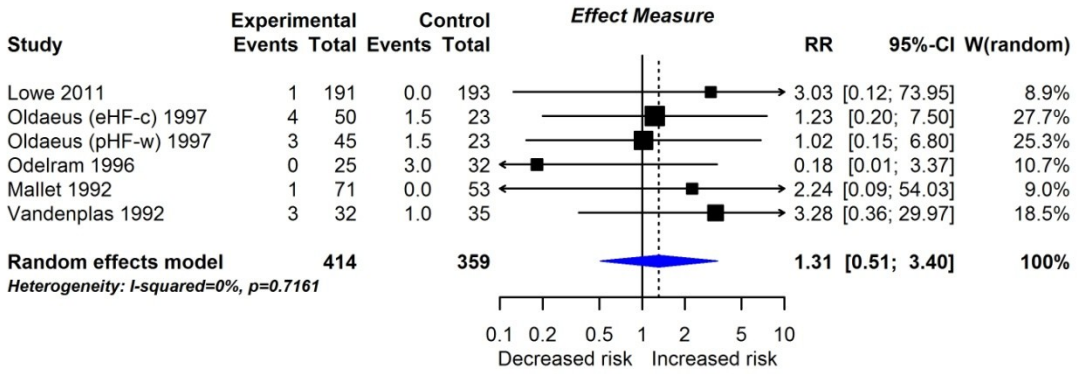


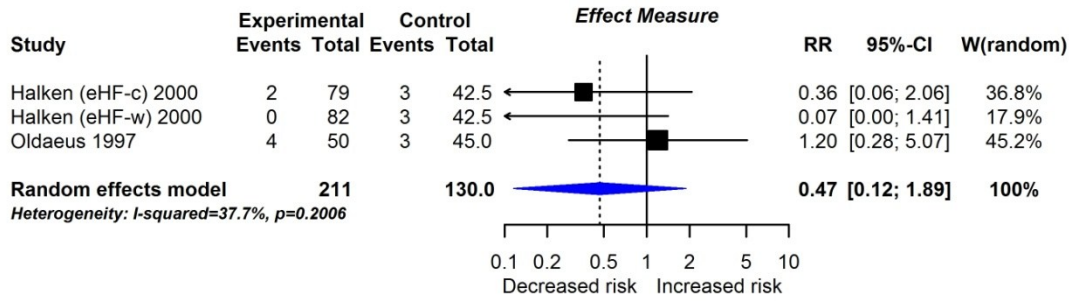
Table 8 Subgroup analysis of Any HF vs CM and CMA risk in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	0	-	-	-
Design – RCT	6	1.31 [0.51- 3.40]	0	
Risk of disease – High	6	1.31 [0.51- 3.40]	0	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF-casein	2	1.42 [0.29-6.86]	0	
HF type – eHF-whey	1	0.18 [0.01-3.37]	-	0.36
HF type – pHF-whey	3	1.85 [0.50-6.87]	0	
Intervention protocol – Formula	6	1.31 [0.51- 3.40]	0	-
Intervention protocol – Multifaceted	0	-	-	
Risk of bias – Low	0	-	-	-
Risk of bias – High/Unclear	6	1.3125 [0.51- 3.40]	0	
Conflict of interest bias – Low	1	0.18 [0.01- 3.37]	-	0.16
Conflict of interest bias – High/Unclear	5	1.66 [0.61- 4.55]	0	

6.10. eHF vs pHF and risk of CMA at age 0-4

Two studies with 3 interventions reported eHF vs pHF and risk of cows milk allergy in children aged 0-4, shown in Figure 60. There is no evidence that the use of eHF reduces CMA risk compared with pHF, with moderate heterogeneity (I^2 = 37.7%).

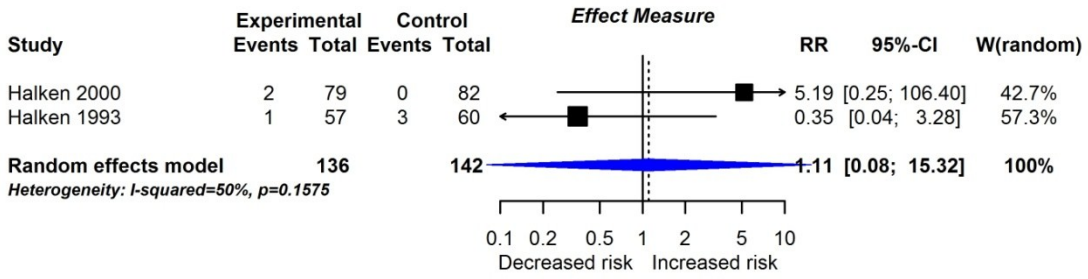
Figure 60 eHF vs pHF for preventing CMA at 0-4 years



6.11. eHF-c vs eHF-w and risk of CMA at age 0-4

Two studies reported eHF-c vs eHF-w and CMA risk in children aged 0-4, shown in Figure 61. There is no evidence that the use of eHF-c reduces CMA risk compared with eHF-w, albeit based on very small nmbers of events, and with significant statistical heterogeneity (I^2 = 50%).

Figure 61 eHF-c vs eHF-w for preventing CMA at 0-4 years



6.12. Short term use of eHF vs CM or HM, and risk of CMA at age 0-4

Two studies reported short term use of eHF vs CM or HM in the first days of life, and risk of cows milk allergy in children aged 0-4, shown in Figures 62 (eHF vs CM_Short) and 63 (eHF vs HM_Short). There is no evidence that the use of eHF for a short period of time reduces CMA risk, in comparison with CM or HM, albeit with moderate statistical heterogeneity (I^2 = 46.4% and 44.1%).

Figure 62 eHF vs CM_Short for preventing CMA at 0-4 years

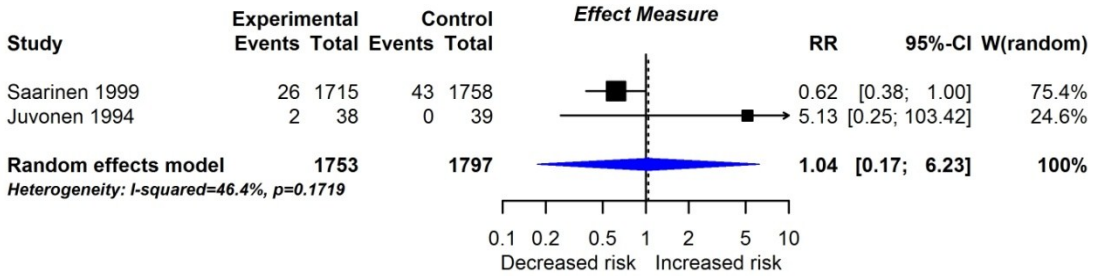
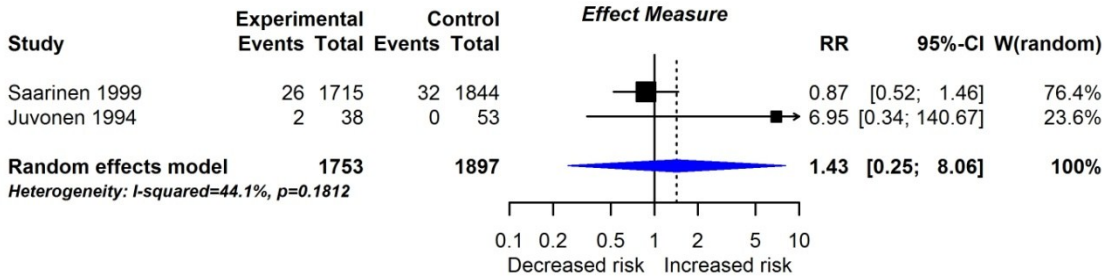


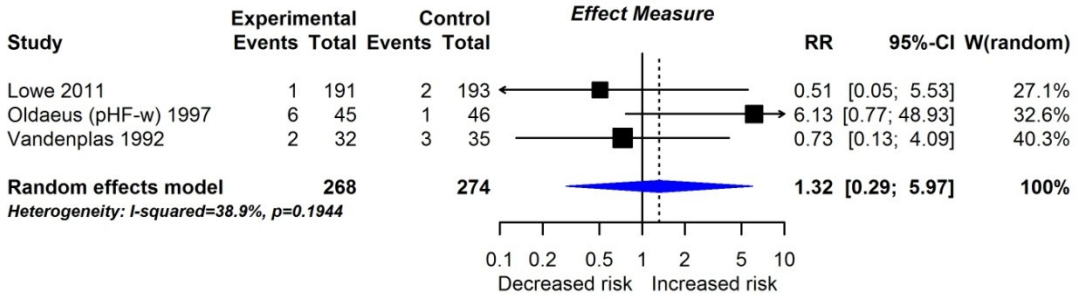
Figure 63 eHF vs HM_Short for preventing CMA at 0-4 years



6.13. pHF vs CM and risk of Egg Allergy at age 0-4

Three studies reported pHF vs CM and risk of egg allergy in children aged 0-4, shown in Figure 64. The pooled data show no evidence of reduced risk of egg allergy, with moderate heterogeneity ($I^2 = 38.9\%$).

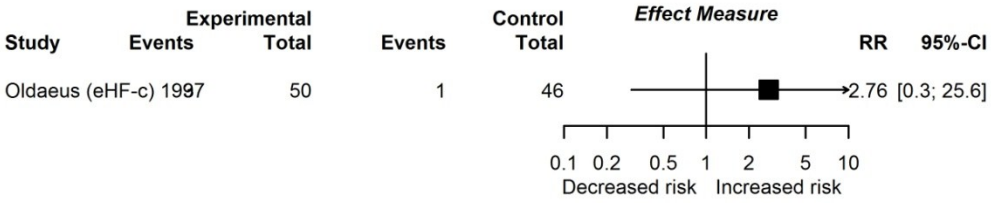
Figure 64 pHF vs CM for preventing Egg Allergy at 0-4 years



6.14. eHF vs CM and risk of Egg Allergy at age 0-4

One study reported eHF vs CM and risk of egg allergy in children aged 0-4, shown in Figure 65. There is no evidence that use of eHF reduces the risk of food allergy in children ages 0-4.

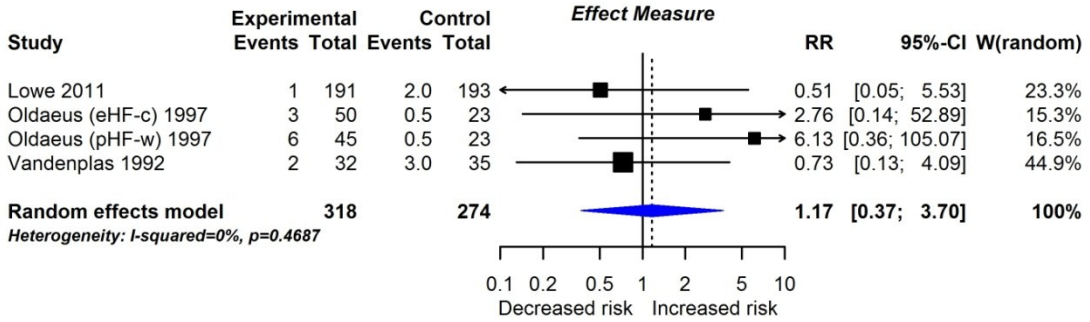
Figure 65 eHF vs CM for preventing Egg Allergy at age 0-4



6.15. Any HF vs CM and risk of Egg Allergy at age 0-4

In total 3 studies with 4 interventions reported AnyHF vs CM and risk of egg allergy in children aged 0-4, shown in Figure 66. The pooled data show no evidence of reduced risk of egg allergy with no statistical heterogenenity ($I^2 = 0\%$).

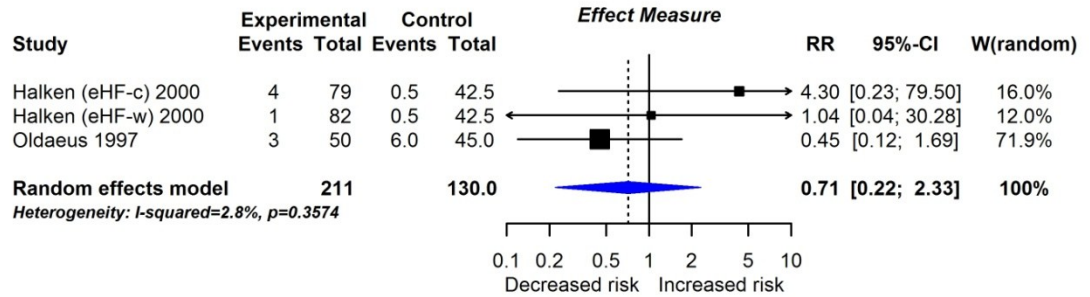
Figure 66 AnyHF vs CM for preventing Egg Allergy at age 0-4



6.16. eHF vs pHF and risk of Egg Allergy at age 0-4

Two studies reported eHF vs pHF and risk of egg allergy in children aged 0-4, shown in Figure 67. There was no evidence of a difference, with low heterogeneity ($I^2 = 2.8\%$).

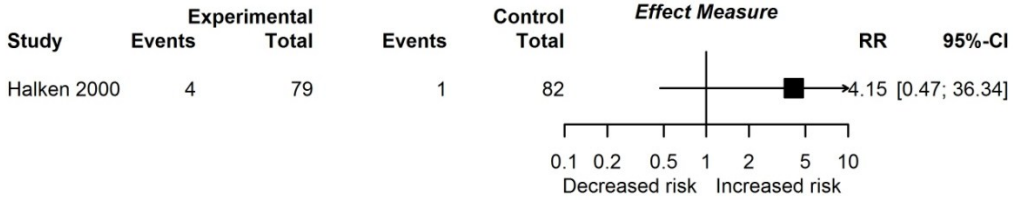
Figure 67 eHF vs pHF for preventing Egg Allergy at 0-4 years



6.17. eHF-c vs eHF-w and risk of Egg Allergy at age 0-4

One study reported eHF-c vs eHF-w and risk of egg allergy in children aged 0-4, shown in Figure 68. There is no evidence that the use of eHF-c reduces the risk of egg allergy but with wide confidence intervals, again due to low numbers of included events.

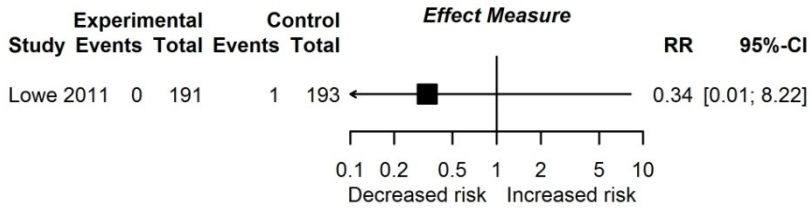
Figure 68 eHF-c vs eHF-w for preventing Egg Allergy at age 0-4



6.18. pHF vs CM and risk of Peanut Allergy (PA) at age 0-4

One study reported pHF vs CM and risk of peanut allergy in children aged 0-4, shown in Figure 69. There is no evidence that the use of pHF reduces the risk of peanut allergy.

Figure 69 pHF vs CM for preventing PA at 0-4 years



6.19. Conclusions

These data were largely derived from studies with high or unclear risk of bias, and high or unclear risk of conflict of interest. All studies other than the brief early interventions were limited to children at high risk of allergic outcomes. There were small numbers of events in most analyses, leading to wide confidence intervals but no evidence that the use of pHF or eHF reduces risk of any food allergy, CMA, egg allergy or PA. One study which used a multifaceted intervention (Zeiger 1989) found reduced risk of any food allergy in the intervention group at aged 0-4, and weak evidence for an effect at age 7. However, the latter was not statistically significant, and no effect was seen in other studies. One large study found weak evidence that short term eHF-casein compared with CM in the first few days of life, reduced CMA risk (Savilahti). However, this was not confirmed in a second study, and was of borderline statistical significance.

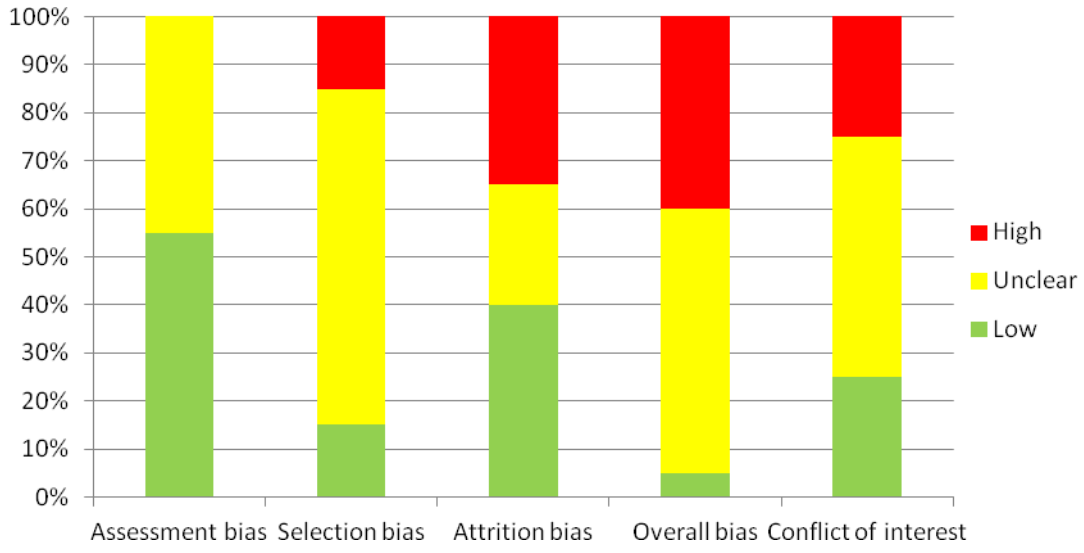
In conclusion we found no evidence that hydrolysed formula reduces food allergy risk.

7. Hydrolysed formula and risk of allergic sensitisation (AS)

Nineteen intervention studies investigated the effect of hydrolysed formula on risk of AS, in over 5500 participants. 40% of studies were considered to be at high risk of bias, mainly due to high attrition bias (>30% of randomised participants not analysed for the outcome). Three quarters of studies had high or unclear risk of conflict of interest, due to possible or probable industry involvement in the study design, analysis or publication (Figure 70).

For analysis of allergic sensitisation, we combined data using sIgE and SPT, and where the same study reported both outcomes we used SPT data preferentially for meta-analysis since in general SPT correlates better with clinical reactivity than sIgE. We also combined data for all age groups, due to the small numbers of studies and limited data available when these analyses were subdivided according to age at outcome. We included total IgE level as an outcome measure, since raised total IgE is associated with other allergic outcomes.

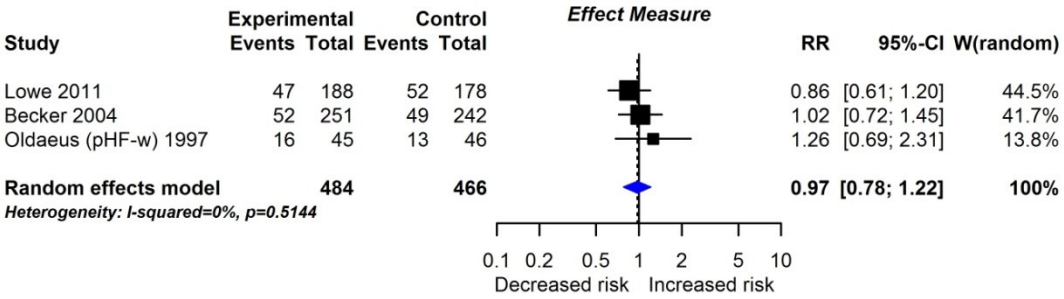
Figure 70 Risk of bias in intervention studies of HF and allergic sensitisation



7.1. pHF vs CM and risk of AS-Any

Three studies reported pHF vs CM and risk of any allergic sensitisation in children of any age, shown in Figure 71. There is no evidence that the use of pHF reduces the risk of allergic sensitisation, with no heterogeneity (I^2 = 0%). All 3 studies reported this outcome at more than one age, but findings were similar at all ages. The GINI study (von Berg) reported sIgE to any allergen at age 10 in 949 children (total of pHF, eHF-c, eHF-w, CM groups). They reported no significant difference between groups, but numerical data were not presented.

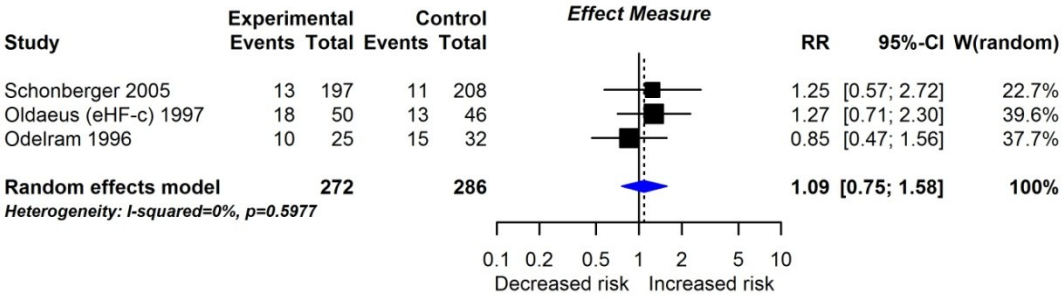
Figure 71 pHF vs CM for preventing AS-Any



7.2. eHF vs CM and risk of AS-Any

Three studies reported eHF vs CM and risk of any allergic sensitisation in children of any age, shown in Figure 72. There is no evidence that the use of eHF reduces the risk of allergic sensitisation, with no heterogeneity (I^2 = 0%). The study of Oldaeus reported this outcome at more than one age, but findings were similar at all ages. The GINI study (von Berg) reported sIgE to any allergen at age 10 in 949 children (total of pHF, eHF-c, eHF-w, CM groups). They reported no significant difference between groups, but numerical data were not presented.

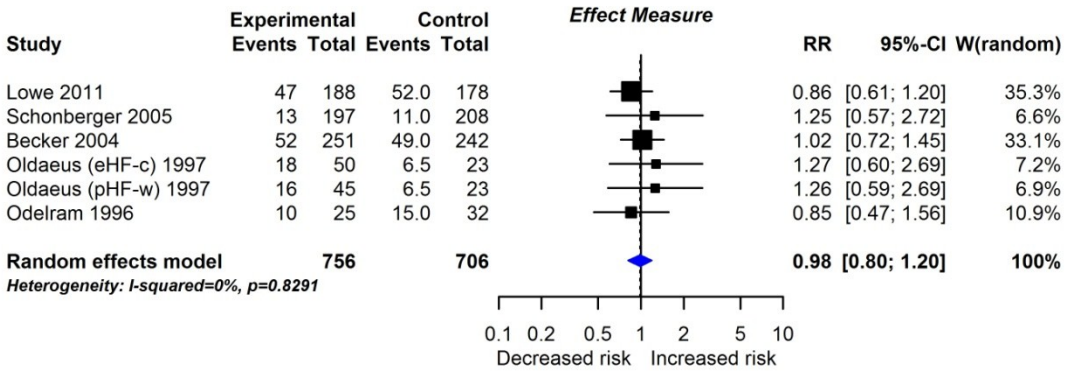
Figure 72 eHF vs CM for preventing AS-Any



7.3. Any HF vs CM and risk of AS-Any

In total 5 studies with 6 interventions reported AnyHF vs CM and risk of any allergic sensitisation in children of any age, shown in Figure 73. There is no evidence that the use of HF reduces the risk of allergic sensitisation, with no heterogeneity (I^2 = 0%). Subgroup analysis (Table 9) did not identify important subgroup differences.

Figure 73 Any HF vs CM for preventing AS-Any



7.4. eHF vs pHF and risk of AS-Any

One study reported eHF vs pHF and risk of AS-Any, shown in Figure 74, with no evidence of difference. A second study - the GINI study (von Berg) reported sIgE to any allergen at age 10 in 949 children (total of pHF, eHF-c, eHF-w, CM groups). They reported no significant difference between groups, but numerical data were not presented.

Figure 74 eHF vs pHF for preventing AS-Any

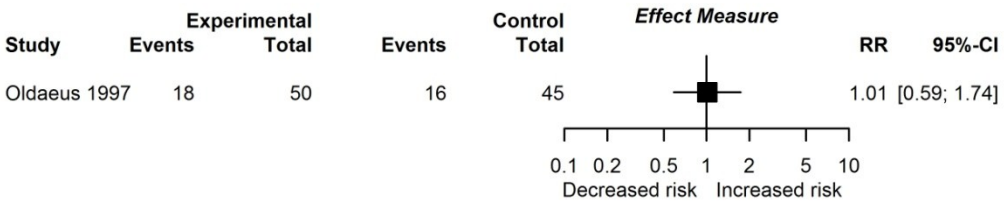


Table 9 Subgroup analysis of Any HF vs CM and AS-Any risk in children of any age

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	0	-	-	-
Design – RCT	6	0.98 [0.80-1.201]	0	
sIgE any	3	1.26 [0.81-1.96]	0	0.21
SPT any	3	0.92 [0.74-1.15]	0	
Risk of disease – High	6	0.98 [0.80-1.20]	0	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF -Casein	1	1.27 [0.60-2.69]	-	0.78
HF type – eHF- Whey	2	0.98 [0.61-1.59]	0	
HF type – pHF-whey	3	0.96 [0.76- 1.20]	0	
Intervention protocol – Formula	4	0.94 [0.72-1.21]	0	0.56
Intervention protocol – Multifaceted	2	1.06 [0.77- 1.45]	0	
Risk of bias – Low	1	1.02 [0.72-1.45]	-	0.78
Risk of bias – High/Unclear	5	0.96 [0.75- 1.23]	0	

Conflict of interest bias – Low	2	0.98 [0.72-1.32]	0	0.96
Conflict of interest bias – High/Unclear	4	0.99 [0.76-1.29]	0	

7.5. pHF vs CM and risk of AS-CM

Seven studies reported pHF vs CM and risk of allergic sensitisation to cow's milk (AS-CM) in children of any age, shown in Figure 75. All studies included participants at high risk of allergic outcomes. The pooled data show no evidence of effect, with no heterogenenity (I^2 = 0%). Lowe and Oldaeus had similar findings at multiple timepoints. Subgroup analyses are shown in Table 10. There was no evidence that study design, multifaceted intervention versus formula alone or risk of bias impacted on study outcomes.

Data not included in meta-analysis

A further 3 studies with over 400 participants reported data on this outcome but could not be included in the meta-analysis. Akimoto, Chan and Moran reported no significant difference in CM sIgE level at 4 months (and 8 months for Moran) between treatment groups.

Figure 75 pHF vs CM for AS-CM

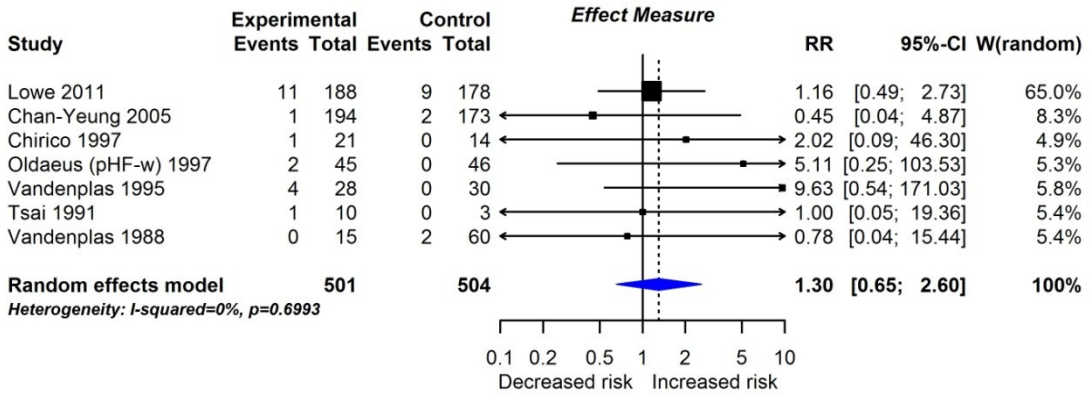


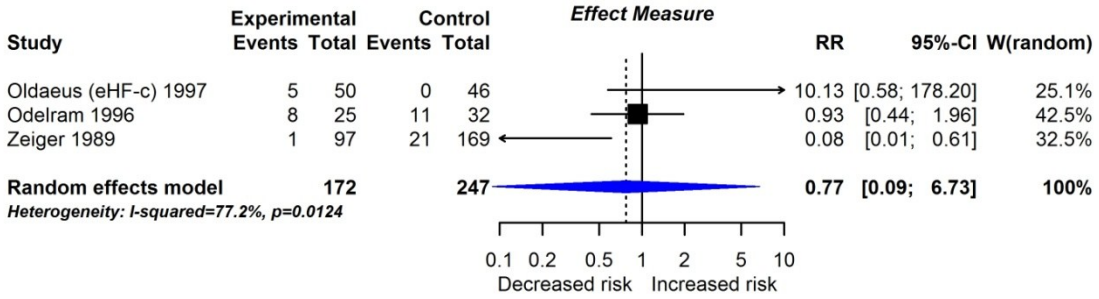
Table 10 Subgroup analysis of pHF vs CM and AS-CM risk in children of any age

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	1	0.78 [0.04-15.44]	-	0.73
Design – RCT	6	1.34 [0.66- 2.73]	0	
sIgE to cows milk	5	0.53 [0.18-1.57]	0	-
SPT to cows milk	5	1.29 [0.62-2.68]	0	
Risk of disease – High	7	1.30 [0.65-2.60]	0	-
Risk of disease – Normal/Low	0	-	-	
Intervention protocol – Formula	5	1.41 [0.67-2.96]	0	0.57
Intervention protocol – Multifaceted	2	0.78 [0.12-5.21]	0	
Overall risk of bias – Low	1	0.45 [0.04-4.87]	-	0.36
Overall risk of bias – High/Unclear	6	1.44 [0.70-2.96]	0	
Conflict of interest bias – Low	1	0.45 [0.04-4.87]	-	0.36
Conflict of interest bias – High/Unclear	6	1.44 [0.70-2.96]	0	

7.6. eHF vs CM and risk of AS-CM

Three studies reported eHF vs CM and risk of AS-CM in children of any age, shown in Figure 76. All studies were in children at high risk of allergic outcomes. There is no evidence of reduced risk of AS-CM with eHF, but with extreme statistical heterogeneity (I^2 = 77.2%). The positive study of Zeiger was a multifaceted study with allergen avoidance measures in mother and infant in addition to use of eHF, which reported a significant difference in AS-CM at 1 year (shown in Figure 76), but no significant difference at 4 years. The study of Oldaeus reported AS-CM at 9 months (shown in Figure 76), and also reported no significant difference at 1.5 years. The study of Mallet (n=177) also reported data for this outcome which were not included in the meta-analysis, using sIgE. The study found no significant difference between groups.

Figure 76 eHF vs CM for preventing AS-CM



7.7. Any HF vs CM and risk of AS-CM

Overall 9 studies reported AnyHF vs CM and risk of AS-CM in children of any age, shown in Figure 77. The pooled data show no evidence of reduced risk of AS-CM, with low heterogenenity (I^2 = 19.3%). A Funnel plot to explore publication bias is shown in Figure 78 and shows no evidence of publication bias (P=0.71). Subgroup analyses are shown in Table 11. There was no evidence that study design, disease risk, multifaceted intervention versus formula alone or hydrolysed formula type or risk of bias impacted on study outcomes and only two studies (Odelram 1996; Chan-Yeung 2005) had a low risk of Conflict of Interest.

Figure 77 Any HF vs CM for preventing AS-CM

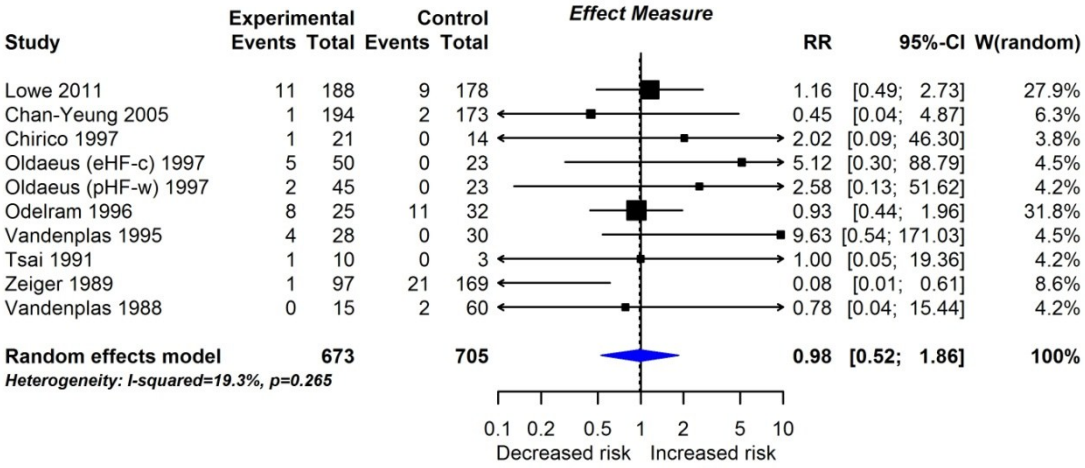
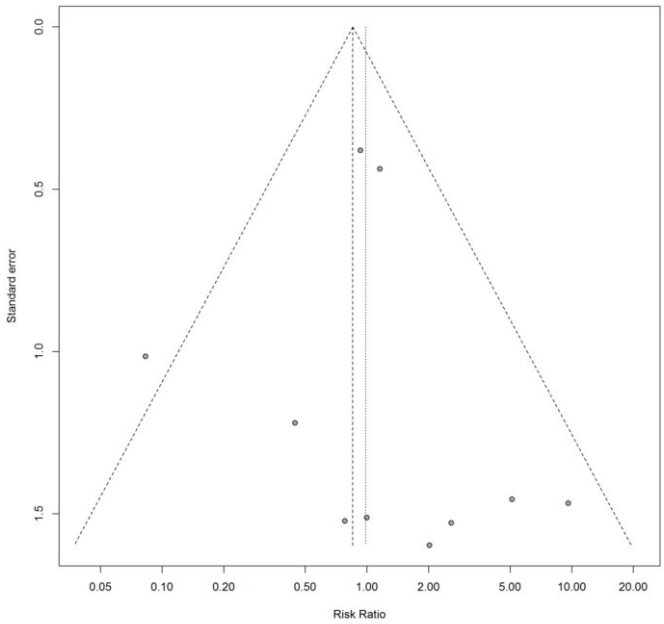


Figure 78 Funnel plot for AnyHF vs CM and AS-CM risk



Egger's Test p-value = 0.71

Table 11 Subgroup analysis of Any HF vs CM and AS-CM

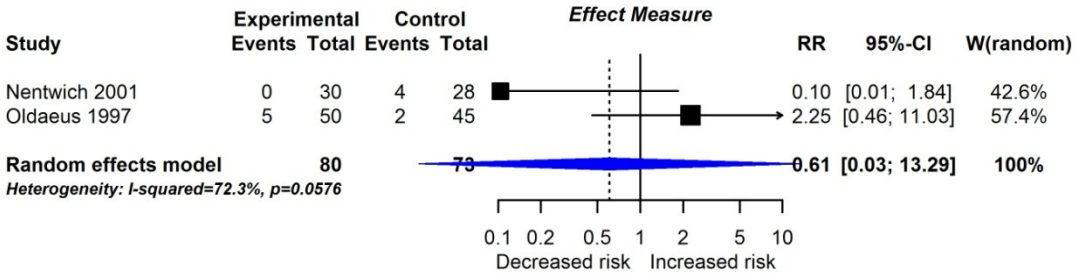
	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	1	0.78 [0.04-15.44]	-	0.87
Design – RCT	9	1.00 [0.49-2.02]	28.2	
SIgE to cows milk	7	0.77 [0.44- 1.35]	0	-
SPT to cows milk	7	1.01 [0.33- 3.09]	45.5	
Risk of disease – High	10	0.98 [0.52- 1.86]	19.3	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF-casein	2	0.57 [0.01- 32.26]	81.5	
HF type – eHF-whey	1	0.93 [0.44- 1.96]	-	0.80
HF type –pHF- whey	7	1.26 [0.63- 2.51]	0	
Intervention protocol – Formula	7	1.18 [0.70- 1.98]	0	0.18
Intervention protocol – Multifaceted	3	0.32 [0.05- 1.98]	40.2	
Overall risk of bias – Low	1	0.45 [0.04- 4.87]	-	0.50
Overall risk of bias – High/Unclear	9	1.05 [0.52- 2.10]	25.5	

Conflict of interest bias – Low	2	0.87 [0.43- 1.78]	0	0.65
Conflict of interest bias – High/Unclear	8	1.16 [0.42- 3.20]	35.2	

7.8. eHF vs pHF and risk of AS-CM

Two studies reported eHF vs pHF and risk of AS-CM in children of any age, shown in Figure 85. There is no evidence that use of eHF prevents AS-CM, however there is high heterogenenity between the studies (I^2 = 72.3%). A further study Scalabrin reported no difference between pHF and eHF groups in AS-CM using sIgE, at ages 3, 5 or 12 months (P=0.63).

Figure 79 eHF vs pHF for preventing AS-CM



Data not included in meta-analysis

Juvonen reported data for short term use of eHF vs CM or HM for AS-CM. They found sIgE antibody levels to cow's milk to be similar in all three of the feeding groups at all ages. The study also found no correlation between IgE levels to cow's milk proteins and the duration of breast-feeding. Schmitz used short term pHF compared with CM, and reported no significant difference between groups in AS-CM at 3, 5 and 12 months.

7.9. HF vs CM and risk of AS-Egg aged 0-4

Four studies reported pHF, and 2 studies eHF vs CM and risk of egg sensitisation (AS-Egg) shown in Figures 80 (pHF), 81 (eHF) and 82. (AnyHF). There is no evidence that HF prevents AS-Egg, with no heterogeneity (I^2 = 0%). Schmitz used short term pHF and measured AS-Egg but data were not reported. Subgroup analyses for AnyHF vs CM are shown in Table 12. There was no evidence for subgroup differences.

Figure 80 pHF vs CM for preventing AS-Egg

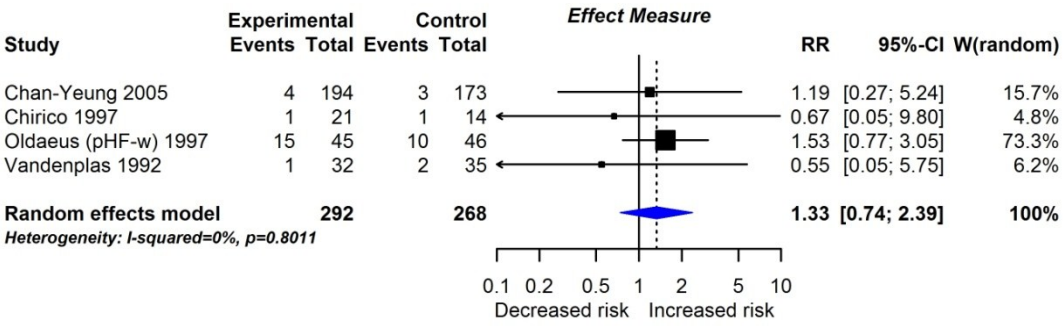


Figure 81 eHF vs CM for preventing AS-Egg

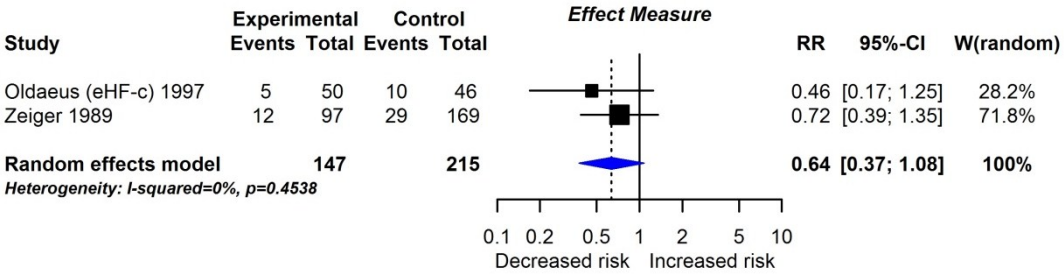


Figure 82 Any HF vs CM for preventing AS-Egg

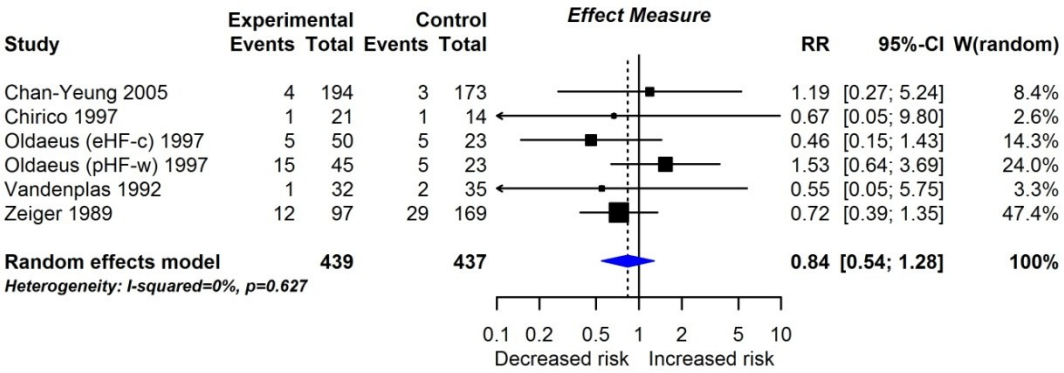


Table 12 Subgroup analysis of any HF vs CM and AS-Egg risk in children of any age

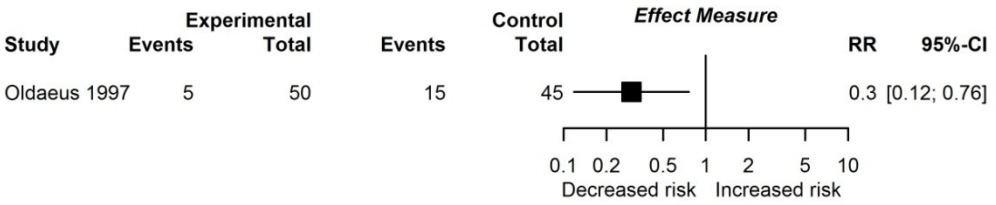
	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Design – qRCT	0	-	-	-
Design – RCT	6	0.84 [0.54-1.29]	0	
sIgE to Egg	4	1.06 [0.44-2.54]	0	-
SPT to Egg	5	0.84 [0.54-1.30]	0	
Risk of disease – High	6	0.84 [0.54-1.28]	0	-
Risk of disease – Normal/Low	0	-	-	
HF type – eHF-Casein	2	0.65 [0.38-1.12]	0	0.15
HF type – pHF-Whey	4	1.25 [0.63-2.51]	0	
Intervention protocol – Formula	3	0.86 [0.36-2.06]	31.3	0.84
Intervention protocol – Multifaceted	3	0.77 [0.44-1.36]	0	
Overall risk of bias – Low	1	1.19 [0.27-5.24]	-	0.63
Overall risk of bias – High/Unclear	5	0.81 [0.52-1.27]	0	

Conflict of interest bias – Low	1	1.19 [0.27-5.24]	-	0.63
Conflict of interest bias – High/Unclear	5	0.81 [0.52-1.27]	0	

7.10. eHF vs pHF and risk of AS-Egg

One study reported eHF vs pHF and risk of AS-Egg in children of any age, shown in Figure 83. Here the use of eHF, when compared to pHF, reduced AS-Egg as measured by SPT at age 9 months. The same study found no difference in AS-Egg measured by sIgE at 18 months.

Figure 83 eHF vs pHF for preventing AS-Egg



Data not included in meta-analysis

Juvonen reported data for short term use of eHF vs CM or HM for AS-Egg. They found sIgE antibody levels to be similar in all three of the feeding groups at all ages studied (4 days, 2 months, 8 months, 1 year and 2 years). However numbers were small such that significant effects cannot be confidently excluded.

7.11. HF vs CM and risk of AS-Peanut

One study reported pHF and one eHF vs CM and risk of allergic sensitisation to peanut (AS-Peanut) in children of any age, shown in Figures 84 (pHF), 85 (eHF) and Figure 86 (AnyHF). There is no evidence that HF reduces this risk. Zeiger reported AS-Peanut at more than one age, but with similar negative findings.

Figure 84 pHF vs CM for preventing AS-Peanut

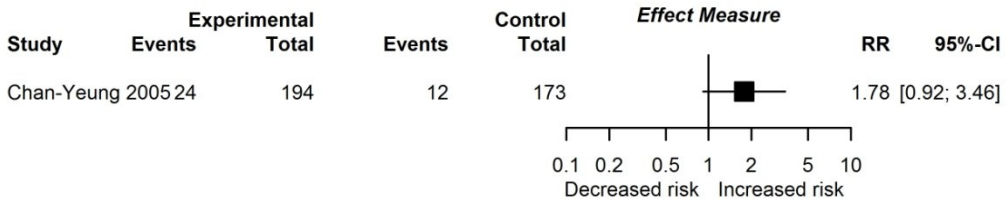


Figure 85 eHF vs CM for preventing AS-Peanut

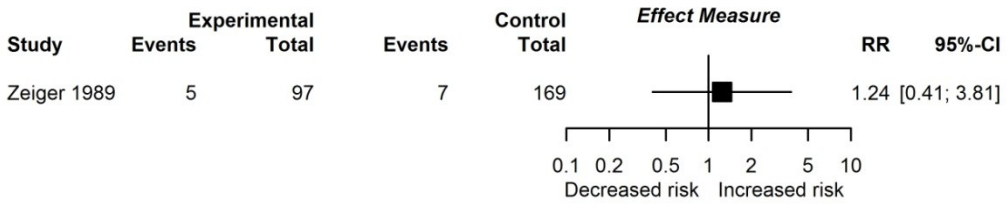
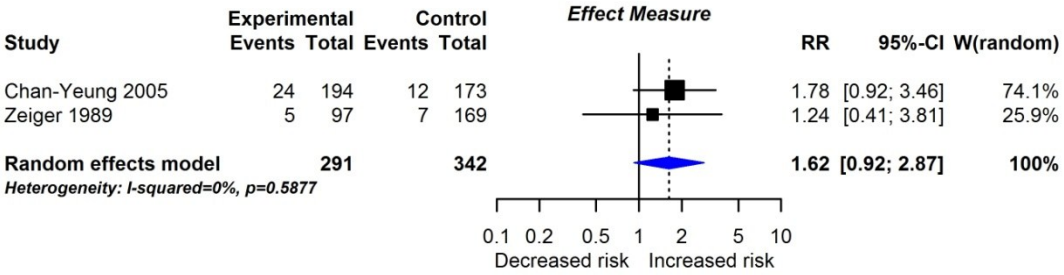


Figure 86 Any HF vs CM for preventing AS-Peanut



7.12. HF vs CM and risk of AS-Food

One study reported pHF and one eHF vs CM and risk of allergic sensitisation to any food (AS-Food) in children of any age, shown in Figures 87 (pHF), 88 (eHF) and 89 (AnyHF). There is some evidence that the use of any HF reduces allergic sensitisation to any food, with no statistical heterogeneity. Zeiger found a difference at 2 years (Figures 88 and 89), but no significant difference in AS-Food at ages 4 and 7. The study of Oldaeus (n=100) could not be included in meta-analysis because numerical data were not reported, but they stated there was no significant difference between groups in cumulative prevalence of any SPT positivity at any age.

Figure 87 pHF vs CM for preventing AS-Food

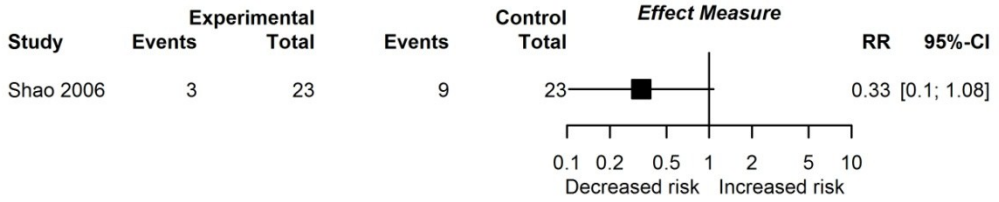


Figure 88 eHF vs CM for preventing AS-Food

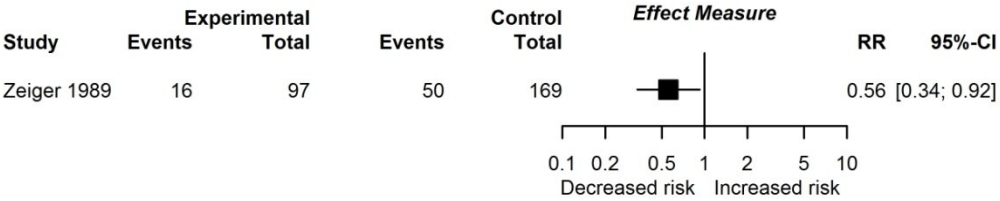
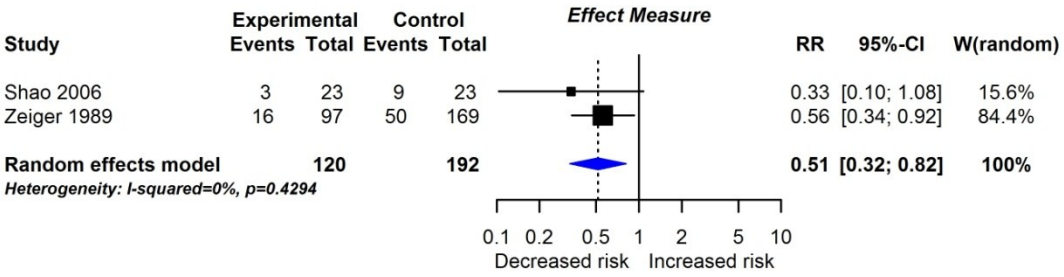


Figure 89 Any HF vs CM for preventing AS-Food



7.13. HF vs CM and risk of AS-aero

One study reported pHF and one eHF vs CM and risk of AS to any aeroallergen (AS-aero), shown in Figures 90 (pHF), 91 (eHF) and 92 (AnyHF). There is no evidence that the use of pHF or eHF reduces AS-aero risk. A third study (Oldaeus n=100) could not be included in either meta-analysis but found no evidence that pHF or eHF influence AS-aero.

Figure 90 pHF vs CM for preventing AS-aero

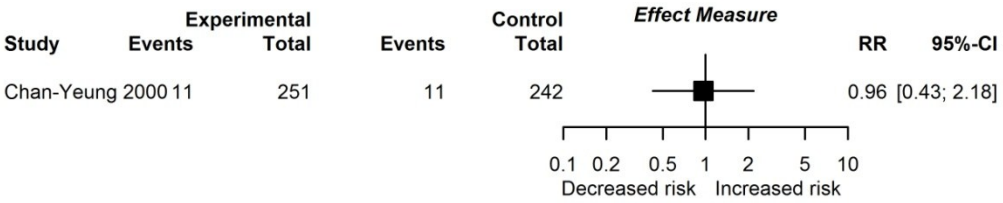


Figure 91 eHF vs CM for preventing AS-aero

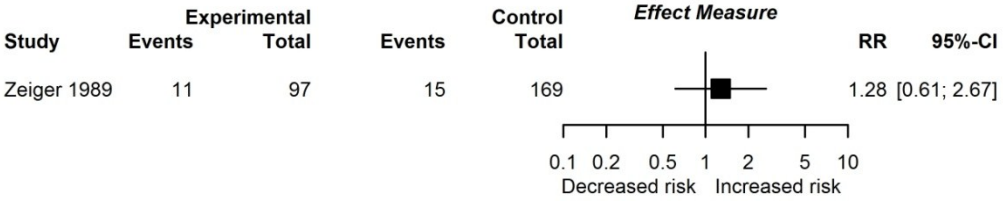
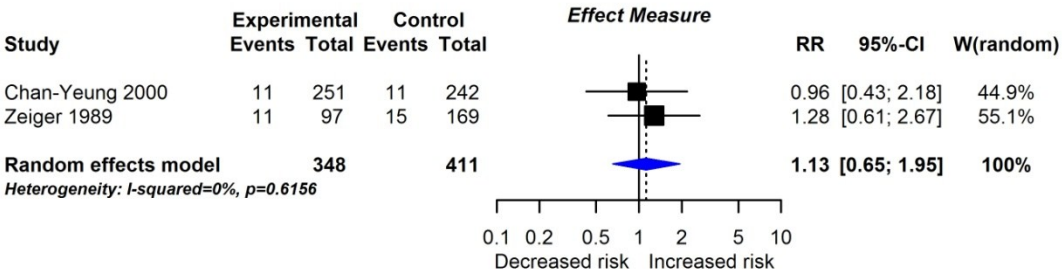


Figure 92 Any HF vs CM for preventing AS-aero

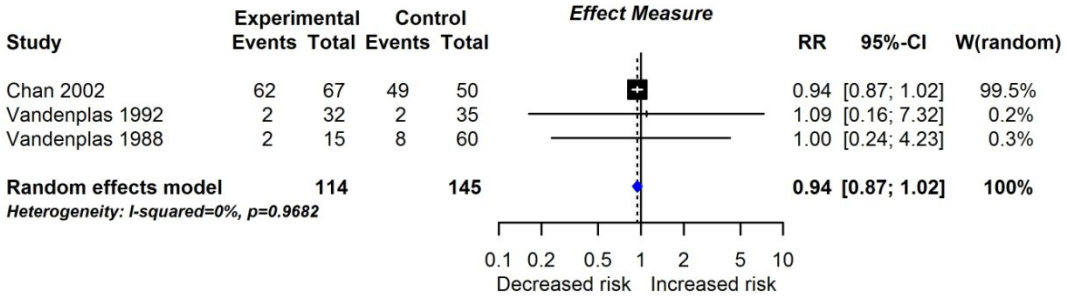


7.14. pHF vs CM and risk of raised Total IgE

Three studies reported pHF vs CM and risk of raised Total IgE in a way that could be included in meta-analysis, shown in Figure 93. There is no evidence that the use of pHF reduces IgE, with no heterogeneity (I^2 = 0%). Four further studies reported pHF effects on IgE but could not be combined in meta-analysis. Akimoto (n~130) found no significant differences between groups in IgE level at 4 months (mean 7.9U/ml intervention, 13.2

control). Tsai (n~33) found no significant difference in IgE level at 2, 6 or 12 months between treatment groups. Chirico (n~35) reported similar IgE levels in each group at 5 days but significantly lower IgE at 6 months in the pHF group (mean 7.6 kU/L) compared with standard formula (mean 28 kU/L).

Figure 93 pHF vs CM raised Total IgE



7.15. eHF vs CM and risk of raised Total IgE

Three studies evaluating eHF vs CM reported Total IgE. Data were not reported that could be combined in meta-analysis. Zeiger reported Total IgE at ages 4 and 7 as similar in eHF and control groups. Schonberger also found no difference between eHF and CM groups at age 2, and Mallet similarly found no difference in IgE at 4 months between treatment groups.

7.16. eHF vs pHF and risk of raised Total IgE

Three studies compared eHF vs pHF. Data could not be meta-analysed. Nentwich found similar IgE levels at 6 months and 1 year between treatment groups. Dupont found no significant difference in IgE at 1 year between groups, although the increase between age 4 months and 1 year was greater in the eHF than pHF group. Scalabrin found no significant difference in IgE between groups at age 4 months and 1 year (P=0.98).

7.17. Other comparisons and risk of raised Total IgE

The studies of Juvonen (n~150) and Schmitz (n~250) evaluated eHF vs CM/HM and pHF vs CM for very early short-term feeding, in relation to Total IgE as an outcome. Juvonen found significantly lower IgE, using a radioimmunoassay, in eHF compared with HM at age 2 months (median 0.7 versus 1.2 kU/L P=0.03) and 4 months (median 1.45 versus 3.0 kU/L P=0.006), and lower IgE in eHF compared with CM at age 4 months (median 1.45 versus

3.35 kU/L P=0.02) but not 2 months. Schmitz (n~250) found a significant difference between the two groups (P=0.02) on day 5, but not on day 1, at month 3 or month 5.

7.18. Conclusions

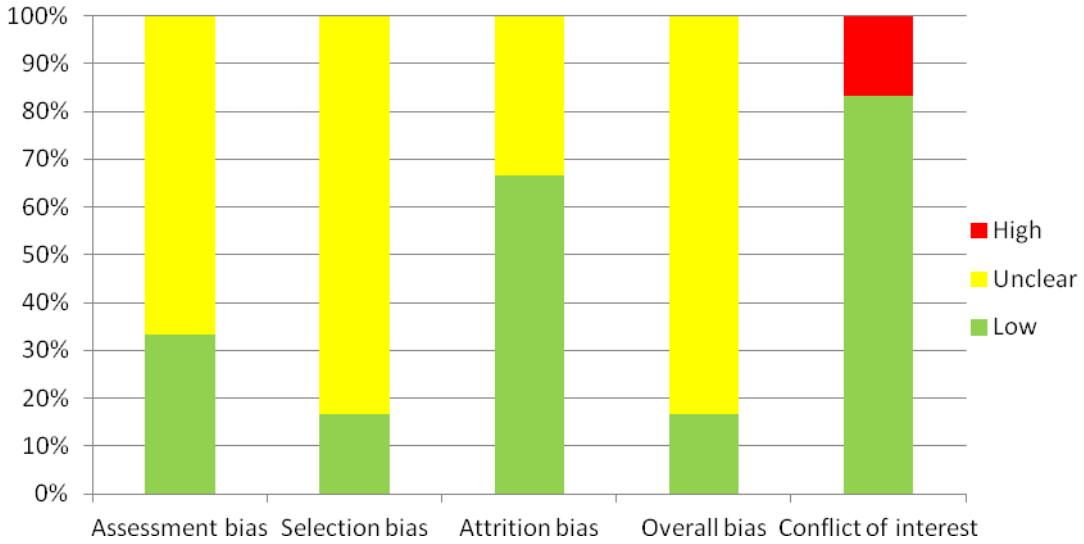
These data were largely derived from studies with high or unclear risk of bias, and high or unclear risk of conflict of interest. For all studies other than the short-term feeding study of Juvonen, participants were at high risk of allergic outcomes. There were small numbers of events in many analyses, leading to wide confidence intervals. Evidence was most conclusive for the outcomes AS-Any and AS-CM. There is no evidence that the use of pHF or eHF reduces risk of allergic sensitisation. One study which used a multifaceted intervention (Zeiger 1989) found reduced risk of AS to CM, and to any food at age 2, but not at age 4 or 7. One qRCT (Juvonen) found evidence that short-term eHF-casein compared with CM or HM in the first few days of life, reduced total IgE up to age 4 months (34). In this study the intervention was for the first 3 days of life, and was followed by exclusive breastfeeding in all intervention groups. The same effect on total IgE was not found in a study of early short-term pHF versus CM.

In conclusion we found no evidence that hydrolysed formula reduces allergic sensitisation.

8. Hydrolysed formula and risk of type I diabetes mellitus (TIDM)

Six intervention studies investigated the effect of hydrolysed formula on risk of TIDM, in over 11,000 participants. Five studies were considered to be at unclear risk of bias, mainly due to unclear selection and/or assessment bias. Five studies were judged to be at low risk of conflict of interest, due to absence of industry involvement in the study design, analysis or publication (Figure 94). Five studies included participants at high risk of TIDM. For outcome analysis of TIDM, we combined data from studies using TIDM-associated antibodies as an outcome measure, with studies using clinical diagnosis or a mixture of clinical diagnosis and serology. We also combined data for all age groups, as with all autoimmune disease analyses. In general the studies used casein-based eHF, but one study (FINDIA – Vaarala) used a whey based eHF formula. There was no evidence that the use of eHF for long or short periods of time reduced the risk of T1DM when compared to CM or HM.

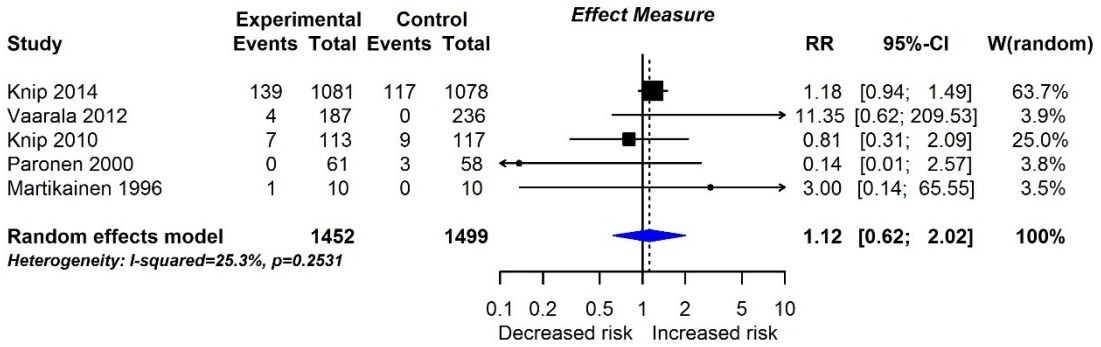
Figure 94 Risk of bias in intervention studies of HF and DM



8.1. eHF vs CM and risk of diabetes in children

Five studies reported eHF vs CM and risk of TIDM, shown in Figure 95. The pooled data show no reduced risk of diabetes but with moderate heterogeneity ($I^2 = 41.9\%$).

Figure 95 eHF vs CM for preventing diabetes



The study of Knip 2010 reported clinical TIDM (shown in Figure 95) and also serological markers of TIDM risk in over 90% of participants who had serological testing at 10 years. Here there was significantly reduced risk of >=1 (HR 0.51 95%CI 0.28, 0.91) and a trend to reduced risk of >=2 (HR 0.47 95%CI 0.19, 1.07) diabetes-associated autoantibodies, with significantly reduced risk for Islet-cell and IA-2, but not Insulin, GAD or ZnT8 antibodies at the same timepoint when assessed individually. Knip 2014 was a similar trial designed to confirm or refute the effect of eHF on TIDM associated autoantibodies, and failed to confirm any effect.

8.2. Short term early feeding with eHF vs CM and TIDM risk

One study reported short term early feeding of eHF vs CM (Figure 96) or eHF vs HM (Figure 97) and risk of TIDM in a normal risk population. Theres was no evidence that the use of eHF for a short period of time (<4 days) reduces TIDM risk.

Figure 96 Short term early feeding with eHF vs CM and TIDM risk

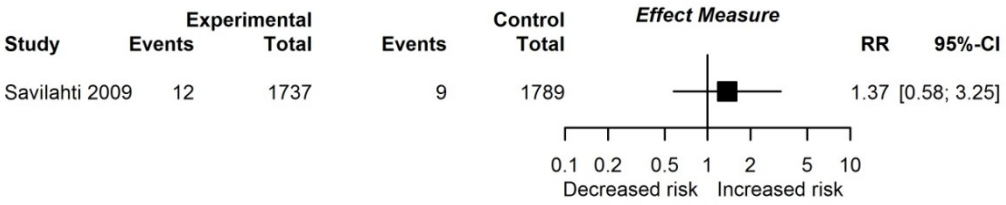
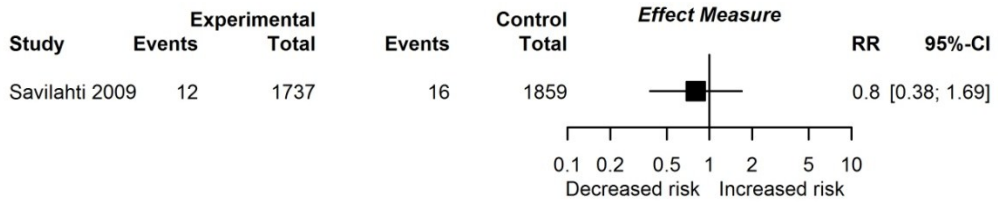


Figure 97 Short term early feeding with eHF vs HM and TIDM risk



8.3. Conclusions

These data were derived from studies with low or unclear risk of bias, and low risk of conflict of interest. For all studies other than the short-term feeding study of Savilahti, participants were at high risk of TIDM. One study used eHF-w (Vaarala), all other studies used eHF-c (Nutramigen, Mead Johnson). We did not identify any studies of pHF for prevention of TIDM. The main analysis (Figure 95) was dominated by one trial reporting serological TIDM, however there was no evidence for different outcomes in the studies reporting clinical TIDM.

In conclusion we found no evidence that hydrolysed formula reduces risk of Type 1 Diabetes Mellitus.

9. General Conclusions

In this systematic review of hydrolysed formula for reducing risk of allergic or autoimmune outcomes, we found no clear evidence for a protective effect with respect to any of the outcomes studied. In general, relatively few included studies carried a low overall risk of bias and low risk of conflict of interest. In particular, the studies in relation to allergic outcomes commonly had unclear or high risk of overall bias, often due to post-randomisation exclusion of participants (attrition bias) and unclear or high risk of conflict of interest due support of the study or investigators by manufacturers of hydrolysed formula. We also found evidence of publication bias, at least in analysis of eczema and recurrent wheeze as outcome measures. This body of evidence should be viewed as pertaining to children at high risk of allergic or autoimmune outcomes, since these accounted for most studies and participants, and almost all analyses were dominated by the findings in high risk children. Thus the evidence base for use of hydrolysed formula in children at 'normal risk' of allergic or autoimmune outcomes is largely unexplored.

In our overview of recent systematic reviews undertaken in 2013, we did not identiy a recent high quality systematic review of hydrolysed formula for preventing allergic or autoimmune disease. However, the updated search on 17th April 2015 identified an updated Cochrane review of hydrolysed formula for allergic outcomes published as an abstract (72). This differed from our review, in that they excluded studies with >80% loss to follow up, and included the outcome 'any allergy'. We elected not to include the outcome 'any allergy' due to its heterogenous definition in different studies, depending on the outcome assessments collected, and the lack of clear evidence that all allergic conditions can be considered to represent a single disease entity. Our review was more inclusive than that of Osborn (72), because we included multifaceted studies if they used HF as part of the intervention, and our search date of 17th April 2015 will have captured more recent studies which their 2013 search did not capture. Osborn did not identify sufficient numbers of studies (maximum 8 trials, in their eczema analysis) to undertake analysis of publication bias. Osborn concluded that there is limited evidence to support a role for hydrolysed formula in reducing 'any allergy' and CMA, but not for other specific allergic outcomes. This is similar to the conclusions of their 2006 Cochrane review. Our findings from a more comprehensive analysis of the literature are

not in agreement with this conclusion – we found no evidence that hydrolysed formula can prevent CMA.

We also identified 2 recent overviews which recommend use of hydrolysed formula to prevent food allergy (73) and all allergy (74) in high risk infants. These reviews did not meet our criteria for data extraction due to low R-AMSTAR scores, and represent overviews of previous work rather than new detailed systematic reviews. It is also worth noting the conclusions of an independent Food and Drug Administration (FDA) review which supported a limited health claim that the Nestlé whey-pHF may reduce eczema risk in high risk infants (71), 'Little scientific evidence suggests that, for healthy infants who are not exclusively breastfed and who have a family history of allergy, feeding a 100 % Whey-Protein Partially Hydrolyzed infant formula from birth up to 4 months of age instead of a formula containing intact cow's milk proteins may reduce the risk of developing atopic dermatitis throughout the 1st year of life'. The FDA approval was based largely on review of the GINI (von Berg) study findings, where Per Protocol analyses rather than Intention To Treat analyses were used to inform the FDA decision. This health claim approval also occurred prior to publication of the study by Lowe which found no significant effect of the Nestlé whey-pHF in a different population. Finally, it is important to note that some trials have been excluded from this review, as also in the Cochrane review, because doubts have been raised about the veracity of the studies and the original trial data have not been verified (75-77).

Taken together our analyses suggest that prior recommendations to use hydrolysed formula in high risk infants for allergy prevention, in place of unhydrolysed cow's milk formula, should be revised. The evidence base for such a recommendation is very weak, with no clear supportive findings for any single allergic outcome and significant risks of publication bias, methodological bias and conflict of interest in relation to studies of hydrolysed formula and allergic outcomes.

10. Acknowlegements

We are grateful to the independent expert peer reviewers Professor Graham Devereux and Dr Carina Venter, and to members of the UK Food Standards Agency, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), and the UK Scientific Advisory Committee on Nutrition for their comments on the study protocol and previous versions of this report. We are grateful to Dr Marialena Trivella and Professor Doug Altman for advice on statistical analysis. We are grateful to Dr Yujie Zhao, Mr Szymon Mikolajewski, Dr Andre Amaral, Dr Mari Kihara, Dr Christian Nielsen, Mr Radoslav Latinovic, Dr Stephanie MacNeill, Dr Andreas Forsters, Dr Daniel Munblit, Dr Sze-Chin Tan, and Dr Claudia Gore for their assistance with translation of foreign language reports. We are grateful to Jackie Cousins of the St. Mary's library at Imperial College London for assistance with literature search training.

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12. Appendix 1 Summary of findings Table

GRADE of evidence assessment								Summary of findings	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**
Intervention: Partially hydrolysed formula vs standard cow's milk formula Outcome: Eczema at age 0-4 Study design: RCT or qRCT									
12 studies	11 RCT 1 qRCT	Serious 11 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	Not serious I2=30.3%, study estimates varying from 0.33 to 1.44; subgroup analysis suggests difference by study design or population	No	Not serious 95% CI for OR do not exclude a clinically important effect, but exclude very large effect sizes and significant harmful effects	No. NB Significant risk when pHF and eHF data are combined. Egger's P<0.05	All RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease	**OR = 0.84 (0.67, 1.07)**	⊗⊗⊗○ **Moderate**
Intervention: Extensively hydrolysed formula vs standard cow's milk formula Outcome: Eczema at age 0-4 Study design: RCT									
6 studies 7 interventions	6 RCT	Serious 5 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	Serious I2=74.4% for analysis of casein-eHF; 0% for whey-eHF. Study estimates varying from 0.18 to 1.26	No	Serious 95% CI for OR do not exclude large beneficial or harmful effects	Not tested (n<10) NB Significant risk when pHF and eHF data are combined. Egger's P<0.05	All RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease	**Casein eHF OR = 0.55 (0.28, 1.09) Whey eHF OR = 1.12 (0.88, 1.42)**	⊗○○○ **Very Low**
Intervention: Partially hydrolysed formula vs standard cow's milk formula Outcome: Recurrent wheeze at age 0-4 Study design: RCT									
5 studies	5 RCT	Serious 4 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	No I2=15.0%, study estimates varying from 0.29 to 1.20	No	Not serious 95% CI for OR do not exclude a clinically important effect, but exclude very large effect sizes	Not tested (n<10) NB Significant risk when pHF and eHF data are combined. Egger's P<0.05	All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease	**OR = 0.82 (0.48, 1.41)**	⊗⊗⊗○ **Moderate**
Intervention: Extensively hydrolysed formula vs standard cow's milk formula Outcome: Recurrent wheeze at age 0-4 Study design: RCT									
5 studies 6 interventions	5 RCT	Serious 5 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	Serious I2=74.4% for analysis of casein-eHF; 0% for whey-eHF. Study estimates varying from 0.18 to 1.26	Not serious 2 studies used multifaceted interventions	Not serious 95% CI for OR do not exclude a clinically important effect, but exclude very large effect sizes	Not tested (n<10) NB Significant risk when pHF and eHF data are combined. Egger's P<0.05	All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease	**Casein eHF OR = 0.76 (0.53, 1.09) Whey eHF OR = 1.15 (0.84, 1.59)**	⊗○○○ **Very Low**

GRADE of evidence assessment								Summary of findings	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**
Intervention: Partially hydrolysed formula vs standard cow's milk formula Outcome: Allergic sensitisation to cow's milk at any age Study design: RCT									
7 studies	7 RCT	Serious 6 studies with high or unclear overall risk of bias, and high/unclear risk of conflict of interest	No I2=0%, study estimates varying from 0.44 to 9.63	Not serious 2 studies used multifaceted interventions	Not serious 95% CI for RR do not exclude a clinically important effect, but exclude very large effect sizes	Not tested (n<10)	All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease	**RR = 1.30 (0.65, 2.60)**	⊗⊗⊗○ **Moderate**
Intervention: Extensively hydrolysed formula vs standard cow's milk formula Outcome: Allergic sensitisation to cow's milk at any age Study design: RCT									
3 studies	3 RCT	Serious All studies with high or unclear overall risk of bias, 2 studies with high/unclear risk of conflict of interest	Serious I2=77.2%, study estimates varying from 0.08 to 10.13	Not serious 1 study used a multifaceted intervention	Serious 95% CI for RR do not exclude large effect sizes	Not tested (n<10)	All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease	**RR = 0.77 (0.09, 6.73)**	⊗○○○ **Very Low**
Intervention: Extensively hydrolysed formula vs standard cow's milk formula Outcome: Type 1 Diabetes Mellitus at any age Study design: RCT									
5 studies	5 RCT	Not serious All studies had low or unclear overall risk of bias, 4 studies had low risk of conflict of interest	Not serious I2=25.3%, study estimates varying from 0.62 to 2.02	No	Not serious 95% CI for RR do not exclude a clinically important effect, but exclude very large effect sizes	Not tested (n<10)	All RCTs were undertaken in populations at high genetic risk of TIDM, and 4 of 5 studies used casein eHF	**RR = 1.12 (0.62, 2.02)**	⊗⊗⊗⊗ **High**

13. Appendix 2 Search Strategies for other systematic reviews

These search strategies were used to identify recent SRs relevant to Reviews A, B or C

Medline

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. Breast Feeding/
6. Milk, Human/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. Infant Formula/
13. Bottle Feeding/
14. wean$.ab,ti.
15. Weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. Weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. Infant Food/
25. Infant Nutritional Physiological Phenomena/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. Breast Feeding/
31. Milk, Human/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. Infant Formula/
38. Bottle Feeding/
39. liquid?.ab,ti.
40. milk.ab,ti.
41. Milk/
42. egg?.ab,ti.
43. Egg Proteins/
44. Egg Proteins, Dietary/

45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.
50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. Nuts/
56. Arachis hypogaea/
57. Prunus/
58. Bertholletia/
59. Juglans/
60. Carya/
61. Pistacia/
62. Anacardium/
63. Corylus/
64. Macadamia/
65. wheat.ab,ti.
66. Triticum/
67. soya.ab,ti.
68. Soybeans/
69. gluten$.ab,ti.
70. Glutens/
71. fish.ab,ti.
72. Fishes/
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. Diet/
75. Diet Therapy/
76. Nutritional Sciences/
77. Child Nutrition Sciences/
78. diet.ab,ti.
79. diets.ab,ti.
80. Diet, Mediterranean/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. Diet, Vegetarian/
90. vegetarian?.ab,ti.
91. vegan$.ab,ti.

92. Diet, Macrobiotic/
93. macrobiotic?.ab,ti.
94. Food/
95. food$.ab,ti.
96. feed.ab,ti.
97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp Cereals/
110. root?.ab,ti.
111. tuber?.ab,ti.
112. exp Vegetables/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. Honey/
135. Fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.

142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.
147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. Nuts/
158. seed?.ab,ti.
159. sesame.ab,ti.
160. mustard.ab,ti.
161. Seeds/
162. exp Meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. Fatty Acids/
173. exp Fatty Acids, Omega-3/
174. exp Fatty Acids, Omega-6/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp Eggs/
184. Bread/
185. bread.ab,ti.
186. oil.ab,ti.
187. oils.ab,ti.
188. oily.ab,ti.
189. omega.ab,ti.
190. exp Seafood/
191. seafood.ab,ti.

192. shellfish.ab,ti.
193. crustacean?.ab,ti.
194. mollusc?.ab,ti.
195. Shellfish/
196. Dairy Products/
197. dairy.ab,ti.
198. exp Milk/
199. milk.ab,ti.
200. Infant Formula/
201. formula?.ab,ti.
202. hydrolysed.ab,ti.
203. Infant Food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp Condiments/
213. Beverages/
214. beverage?.ab,ti.
215. fluid intake.ab,ti.
216. water.ab,ti.
217. drink$.ab,ti.
218. exp Food Preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. Cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.

242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.
247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. exp Dietary Carbohydrates/
284. exp Dietary Fats/
285. exp Dietary Fiber/
286. exp Dietary Proteins/
287. exp Dietary Supplements/
288. exp Food Additives/
289. exp Vitamins/
290. supplements.ab,ti.
291. supplement.ab,ti.

292. vitamin$.ab,ti.
293. retinol.ab,ti.
294. carotenoid$.ab,ti.
295. tocopherol.ab,ti.
296. folate$.ab,ti.
297. folic acid.ab,ti.
298. methionine.ab,ti.
299. riboflavin.ab,ti.
300. thiamine.ab,ti.
301. niacin.ab,ti.
302. pyridoxine.ab,ti.
303. cobalamin.ab,ti.
304. mineral$.ab,ti.
305. sodium.ab,ti.
306. iron.ab,ti.
307. calcium.ab,ti.
308. selenium.ab,ti.
309. iodine.ab,ti.
310. magnesium.ab,ti.
311. potassium.ab,ti.
312. zinc.ab,ti.
313. copper.ab,ti.
314. phosphorus.ab,ti.
315. manganese.ab,ti.
316. chromium.ab,ti.
317. phytochemical.ab,ti.
318. polyphenol$.ab,ti.
319. phytoestrogen$.ab,ti.
320. genistein.ab,ti.
321. saponin$.ab,ti.
322. coumarin$.ab,ti.
323. flavonoid$.ab,ti.
324. polyphenol$.ab,ti.
325. flavonol$.ab,ti.
326. flavone$.ab,ti.
327. isoflavone$.ab,ti.
328. catechin$.ab,ti.
329. ascorbic acid$.ab,ti.
330. hydroxy cholecalciferol$.ab,ti.
331. hydroxycholecalciferol$.ab,ti.
332. tocotrienol$.ab,ti.
333. carotene$.ab,ti.
334. cryptoxanthin$.ab,ti.
335. lycopene$.ab,ti.
336. lutein$.ab,ti.
337. zeaxanthin$.ab,ti.
338. selenium$.ab,ti.
339. organic diet?.ab,ti.
340. Food, Organic/

341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg$.ab,ti.
343. asthma$.ab,ti.
344. wheeze.ab,ti.
345. wheezing.ab,ti.
346. bronchial hyperresponsiveness.ab,ti.
347. bronchial hyperreactivity.ab,ti.
348. Forced expiratory volume.ab,ti.
349. FEV1.ab,ti.
350. "FEV 1".ab,ti.
351. "FEV0.5".ab,ti.
352. "FEV 0.5".ab,ti.
353. Forced vital capacity.ab,ti.
354. FVC.ab,ti.
355. Peak expiratory flow rate.ab,ti.
356. PEFR.ab,ti.
357. eczema.ab,ti.
358. neurodermatitis.ab,ti.
359. rhinitis.ab,ti.
360. besniers prurigo.ab,ti.
361. rhinoconjunctivitis.ab,ti.
362. hayfever.ab,ti.
363. (hay adj fever).ab,ti.
364. poll?nosis.ab,ti.
365. SAR.ab,ti.
366. (pollen adj allergy).ab,ti.
367. conjunctivitis.ab,ti.
368. immunoglobulin e.ab,ti.
369. Total IgE.ab,ti.
370. autoimmune disease?.ab,ti.

371. diabetes.ab,ti.
372. diabetic.ab,ti.
373. type 1.ab,ti.
374. c?eliac disease.ab,ti.
375. crohn$ disease.ab,ti.
376. Inflammatory Bowel Disease?.ab,ti.
377. Ulcerative colitis.ab,ti.
378. (Lympho$ adj3 thyroiditi$).ab,ti.
379. (Thyroiditi$ adj3 autoimmune).ab,ti.
380. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
381. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
382. Graves? disease.ab,ti.
383. Basedow$ disease.ab,ti.
384. exophthalmic goiter?.ab,ti.
385. (Still? Disease adj3 (juvenile or onset)).ab,ti.
386. (Juvenile adj3 arthriti$).ab,ti.
387. vitiligo.ab,ti.
388. Psorias?s.ab,ti.
389. (Arthriti? adj3 Psoria$).ab,ti.
390. atopic disease.ab,ti.
391. atopic dermatitis.ab,ti.
392. (food? adj3 sensiti$).ab,ti.
393. (food? adj3 toleran$).ab,ti.
394. (food? adj3 intoleran$).ab,ti.
395. ((aero or air$) adj3 allergen?).ab,ti.
396. (aeroallergen? adj3 sensiti$).ab,ti.
397. (allergen? adj3 sensiti$).ab,ti.
398. skin prick test$.ab,ti.
399. atopy.ab,ti.
400. hypersensitiv$.ab,ti.
401. Hypersensitivity/
402. exp Food Hypersensitivity/
403. Respiratory Hypersensitivity/
404. Asthma/
405. Bronchial Hyperreactivity/
406. Forced Expiratory Volume/
407. Vital Capacity/
408. Peak Expiratory Flow Rate/
409. Eczema/
410. Neurodermatitis/
411. Rhinitis/
412. Rhinitis, Allergic, Perennial/
413. Rhinitis, Allergic, Seasonal/
414. Conjunctivitis/
415. Immunoglobulin E/
416. Autoimmune Diseases/
417. Diabetes Mellitus, Type 1/
418. Celiac Disease/
419. Crohn Disease/
420. Inflammatory Bowel Diseases/

421. Colitis, Ulcerative/
422. Thyroiditis, Autoimmune/
423. Hashimoto Disease/
424. Postpartum Thyroiditis/
425. Graves Disease/
426. Arthritis, Juvenile Rheumatoid/
427. Vitiligo/
428. Psoriasis/
429. Arthritis, Psoriatic/
430. Dermatitis, Atopic/
431. Hypersensitivity, Immediate/
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant?.ab,ti.
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
436. 434 or 435
437. (old or age?).ab,ti.
438. 436 and 437
439. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
440. ((first or second or two) adj3 "year? of life").ab,ti.
441. Infant/
442. Infant, Newborn/
443. (maternal adj7 pregnan$).ab,ti.
444. (maternal adj7 lactat$).ab,ti.
445. (mother? adj7 pregnan$).ab,ti.
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. MEDLINE.tw.
448. systematic review.tw.
449. meta-analysis.pt.
450. intervention$.ti.
451. 447 or 448 or 449 or 450
452. 16 or 73 or 341
453. 432 and 446 and 451 and 452
454. limit 453 to yr="2011 -Current"

Embase

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. breast feeding/
6. breast milk/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. artificial milk/
13. bottle feeding/
14. wean$.ti,ab.
15. weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. baby food/
25. infant nutrition/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. breast feeding/
31. breast milk/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. artificial milk/
38. bottle feeding/
39. liquid?.ti,ab.
40. milk.ti,ab.
41. milk/
42. egg?.ti,ab.
43. egg/
44. egg protein/
45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.

50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. nut/
56. peanut/
57. almond/
58. Brazil nut/
59. exp walnut/
60. pecan/
61. pistachio/
62. cashew nut/
63. hazelnut/
64. Corylus avellana/
65. Macadamia/
66. wheat.ti,ab.
67. exp wheat/
68. soya.ti,ab.
69. soybean/
70. gluten$.ti,ab.
71. gluten/
72. fish$.ti,ab.
73. fish/
74. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75. diet/
76. diet therapy/
77. nutritional science/
78. diet.ti,ab.
79. diets.ti,ab.
80. Mediterranean diet/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. vegetarian diet/
90. vegetarian?.ti,ab.
91. vegan$.ti,ab.
92. macrobiotic diet/
93. macrobiotic?.ti,ab.
94. food/
95. food$.ab,ti.
96. feed.ab,ti.

97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp cereal/
110. root?.ti,ab.
111. tuber?.ti,ab.
112. exp vegetable/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. honey/
135. fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.
142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.

147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. exp nut/
158. seed?.ti,ab.
159. sesame.ti,ab.
160. mustard.ti,ab.
161. plant seed/
162. meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. fatty acid/
173. omega 3 fatty acid/
174. omega 6 fatty acid/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp egg/
184. bread/
185. bread.ti,ab.
186. oil.ti,ab.
187. oils.ti,ab.
188. oily.ti,ab.
189. omega.ti,ab.
190. sea food/
191. seafood.ti,ab.
192. shellfish.ti,ab.
193. crustacean?.ti,ab.
194. mollusc?.ti,ab.
195. shellfish/
196. exp dairy product/

197. dairy.ti,ab.
198. milk/
199. milk.ti,ab.
200. artificial milk/
201. formula?.ti,ab.
202. hydrolysed.ti,ab.
203. baby food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp condiment/
213. beverage/
214. beverage?.ti,ab.
215. fluid intake.ti,ab.
216. water.ti,ab.
217. drink$.ti,ab.
218. exp food preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.
242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.

247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. carbohydrate diet/
284. carbohydrate intake/
285. fat intake/
286. dietary fiber/
287. protein intake/
288. diet supplementation/
289. food additive/
290. exp vitamin/
291. supplements.ab,ti.
292. supplement.ab,ti.
293. vitamin$.ab,ti.
294. retinol.ab,ti.
295. carotenoid$.ab,ti.
296. tocopherol.ab,ti.

297. folate$.ab,ti.
298. folic acid.ab,ti.
299. methionine.ab,ti.
300. riboflavin.ab,ti.
301. thiamine.ab,ti.
302. niacin.ab,ti.
303. pyridoxine.ab,ti.
304. cobalamin.ab,ti.
305. mineral$.ab,ti.
306. sodium.ab,ti.
307. iron.ab,ti.
308. calcium.ab,ti.
309. selenium.ab,ti.
310. iodine.ab,ti.
311. magnesium.ab,ti.
312. potassium.ab,ti.
313. zinc.ab,ti.
314. copper.ab,ti.
315. phosphorus.ab,ti.
316. manganese.ab,ti.
317. chromium.ab,ti.
318. phytochemical.ab,ti.
319. polyphenol$.ab,ti.
320. phytoestrogen$.ab,ti.
321. genistein.ab,ti.
322. saponin$.ab,ti.
323. coumarin$.ab,ti.
324. flavonoid$.ab,ti.
325. polyphenol$.ab,ti.
326. flavonol$.ab,ti.
327. flavone$.ab,ti.
328. isoflavone$.ab,ti.
329. catechin$.ab,ti.
330. ascorbic acid$.ab,ti.
331. hydroxy cholecalciferol$.ab,ti.
332. hydroxycholecalciferol$.ab,ti.
333. tocotrienol$.ab,ti.
334. carotene$.ab,ti.
335. cryptoxanthin$.ab,ti.
336. lycopene$.ab,ti.
337. lutein$.ab,ti.
338. zeaxanthin$.ab,ti.
339. selenium$.ab,ti.
340. organic diet?.ab,ti.
341. organic food/
342. 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or

144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341
343. allerg$.ab,ti.
344. asthma$.ab,ti.
345. wheeze.ab,ti.
346. wheezing.ab,ti.
347. bronchial hyperresponsiveness.ab,ti.
348. bronchial hyperreactivity.ab,ti.
349. Forced expiratory volume.ab,ti.
350. FEV1.ab,ti.
351. "FEV 1".ab,ti.
352. "FEV0.5".ab,ti.
353. "FEV 0.5".ab,ti.
354. Forced vital capacity.ab,ti.
355. FVC.ab,ti.
356. Peak expiratory flow rate.ab,ti.
357. PEFR.ab,ti.
358. eczema.ab,ti.
359. neurodermatitis.ab,ti.
360. rhinitis.ab,ti.
361. besniers prurigo.ab,ti.
362. rhinoconjunctivitis.ab,ti.
363. hayfever.ab,ti.
364. (hay adj fever).ab,ti.
365. poll?nosis.ab,ti.
366. SAR.ab,ti.
367. (pollen adj allergy).ab,ti.
368. conjunctivitis.ab,ti.
369. immunoglobulin e.ab,ti.
370. Total IgE.ab,ti.
371. autoimmune disease?.ab,ti.
372. diabetes.ab,ti.
373. diabetic.ab,ti.
374. type 1.ab,ti.
375. c?eliac disease.ab,ti.
376. crohn$ disease.ab,ti.

377. Inflammatory Bowel Disease?.ab,ti.
378. Ulcerative colitis.ab,ti.
379. (Lympho$ adj3 thyroiditi$).ab,ti.
380. (Thyroiditi$ adj3 autoimmune).ab,ti.
381. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
382. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
383. Graves? disease.ab,ti.
384. Basedow$ disease.ab,ti.
385. exophthalmic goiter?.ab,ti.
386. (Still? Disease adj3 (juvenile or onset)).ab,ti.
387. (Juvenile adj3 arthriti$).ab,ti.
388. vitiligo.ab,ti.
389. Psorias?s.ab,ti.
390. (Arthriti? adj3 Psoria$).ab,ti.
391. atopic disease.ab,ti.
392. atopic dermatitis.ab,ti.
393. (food? adj3 sensiti$).ab,ti.
394. (food? adj3 toleran$).ab,ti.
395. (food? adj3 intoleran$).ab,ti.
396. ((aero or air$) adj3 allergen?).ab,ti.
397. (aeroallergen? adj3 sensiti$).ab,ti.
398. (allergen? adj3 sensiti$).ab,ti.
399. skin prick test$.ab,ti.
400. atopy.ab,ti.
401. hypersensitiv$.ab,ti.
402. exp hypersensitivity/
403. respiratory tract allergy/
404. asthma/
405. wheezing/
406. bronchus hyperreactivity/
407. forced expiratory volume/
408. forced vital capacity/
409. peak expiratory flow/
410. eczema/
411. neurodermatitis/
412. rhinitis/
413. rhinoconjunctivitis/
414. hay fever/
415. pollen allergy/
416. perennial rhinitis/
417. conjunctivitis/
418. immunoglobulin E/
419. autoimmune disease/
420. diabetes mellitus/
421. insulin dependent diabetes mellitus/
422. celiac disease/
423. Crohn disease/
424. enteritis/
425. ulcerative colitis/
426. autoimmune thyroiditis/

427. Hashimoto disease/
428. postpartum thyroiditis/
429. Graves disease/
430. juvenile rheumatoid arthritis/
431. vitiligo/
432. psoriasis/
433. psoriatic arthritis/
434. atopic dermatitis/
435. nutritional intolerance/
436. 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431 or 432 or 433 or 434 or 435
437. infant?.ab,ti.
438. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
439. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
440. 438 or 439
441. (old or age?).ab,ti.
442. 440 and 441
443. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
444. ((first or second or two) adj3 "year? of life").ab,ti.
445. infant/
446. newborn/
447. (maternal adj7 pregnan$).ti,ab.
448. (maternal adj7 lactat$).ti,ab.
449. (mother? adj7 pregnan$).ti,ab.
450. 437 or 442 or 443 or 444 or 445 or 446 or 447 or 448 or 449
451. MEDLINE.tw.
452. exp systematic review/
453. systematic review.tw.
454. meta analysis/
455. intervention$.ti.
456. 451 or 452 or 453 or 454 or 455
457. 16 or 74 or 342
458. 436 and 450 and 456 and 457
459. limit 458 to yr="2011 -Current"

COCHRANE Reviews and DARE

1. “breast feeding”:ab,ti
2. breastfeeding:ab,ti
3. “breast fed”:ab,ti
4. breastfed:ab,ti
5. MeSH descriptor [Breast Feeding] this term only
6. MeSH descriptor [Milk, Human] this term only
7. formula*:ab,ti
8. hydrolysed:ab,ti
9. bottlefed:ab,ti
10. “bottle fed”:ab,ti
11. (bottle NEAR/3 feed*):ab,ti
12. MeSH descriptor [Infant Formula] this term only
13. MeSH descriptor [Bottle Feeding] this term only
14. wean*:ab,ti
15. MeSH descriptor [Weaning] this term only
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. “complementary food*”:ab,ti
18. (introduc* NEAR/2 food*):ab,ti
19. wean*:ab,ti
20. MeSH descriptor [Weaning] this term only
21. solid*:ab,ti
22. semi-solid*:ab,ti
23. “baby food*”:ab,ti
24. MeSH descriptor [Infant Food] this term only
25. MeSH descriptor [Infant Nutritional Physiological Phenomena] this term only
26. “breast feeding”:ab,ti
27. breastfeeding:ab,ti
28. “breast fed”:ab,ti
29. breastfed:ab,ti
30. MeSH descriptor [Breast Feeding] this term only
31. MeSH descriptor [Milk, Human] this term only
32. formula*:ab,ti
33. hydrolysed:ab,ti
34. bottlefed:ab,ti
35. “bottle fed”:ab,ti
36. (bottle NEAR/3 feed*):ab,ti
37. MeSH descriptor [Infant Formula] this term only
38. MeSH descriptor [Bottle Feeding] this term only
39. liquid*:ab,ti
40. milk:ab,ti
41. MeSH descriptor [Milk] this term only
42. egg*:ab,ti
43. MeSH descriptor [Egg Proteins] this term only
44. MeSH descriptor [Egg Proteins, Dietary] this term only
45. nut*:ab,ti
46. peanut*:ab,ti
47. almond*:ab,ti
48. (brazil* NEAR/5 nut*):ab,ti
49. walnut*:ab,ti

50. pecan*:ab,ti
51. pistachio*:ab,ti
52. cashew*:ab,ti
53. hazelnut*:ab,ti
54. macadamia*:ab,ti
55. Nuts] this term only
56. MeSH descriptor [Arachis hypogaea] this term only
57. MeSH descriptor [Prunus] this term only
58. MeSH descriptor [Bertholletia] this term only
59. MeSH descriptor [Juglans] this term only
60. MeSH descriptor [Carya] this term only
61. MeSH descriptor [Pistacia] this term only
62. MeSH descriptor [Anacardium] this term only
63. MeSH descriptor [Corylus] this term only
64. MeSH descriptor [Macadamia] this term only
65. wheat:ab,ti
66. MeSH descriptor [Triticum] this term only
67. soya:ab,ti
68. MeSH descriptor [Soybeans] this term only
69. gluten*:ab,ti
70. MeSH descriptor [Glutens] this term only
71. fish:ab,ti
72. MeSH descriptor [Fishes] this term only
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. MeSH descriptor [Diet] this term only
75. MeSH descriptor [Diet Therapy] this term only
76. MeSH descriptor [Nutritional Sciences] this term only
77. MeSH descriptor [Child Nutrition Sciences] this term only
78. diet:ab,ti
79. diets:ab,ti
80. MeSH descriptor [Diet, Mediterranean] this term only
81. “mediterranean diet*”:ab,ti
82. dietetic:ab,ti
83. dietary:ab,ti
84. eat:ab,ti
85. eating:ab,ti
86. intake:ab,ti
87. nutrient*:ab,ti
88. nutrition:ab,ti
89. MeSH descriptor [Diet, Vegetarian] this term only
90. vegetarian*:ab,ti
91. vegan*:ab,ti
92. MeSH descriptor [Diet, Macrobiotic] this term only
93. macrobiotic*:ab,ti
94. MeSH descriptor [Food] this term only
95. food*:ab,ti
96. feed:ab,ti

97. feeding:ab,ti
98. cereal*:ab,ti
99. grain*:ab,ti
100. granary:ab,ti
101. wholegrain:ab,ti
102. wholewheat:ab,ti
103. “whole wheat”:ab,ti
104. wheat:ab,ti
105. wheatgerm:ab,ti
106. rye:ab,ti
107. barley:ab,ti
108. oat*:ab,ti
109. MeSH descriptor [Cereals] explode all trees
110. root*:ab,ti
111. tuber*:ab,ti
112. MeSH descriptor [Vegetables] explode all trees
113. vegetable*:ab,ti
114. onion*:ab,ti
115. spinach:ab,ti
116. chard:ab,ti
117. tomato*:ab,ti
118. pepper*:ab,ti
119. carrot*:ab,ti
120. beetroot:ab,ti
121. asparagus:ab,ti
122. garlic:ab,ti
123. pumpkin:ab,ti
124. sprouts:ab,ti
125. broccoli:ab,ti
126. cabbage*:ab,ti
127. celery:ab,ti
128. ginger:ab,ti
129. potato*:ab,ti
130. crisps:ab,ti
131. fries:ab,ti
132. syrup:ab,ti
133. honey:ab,ti
134. MeSH descriptor [Honey] this term only
135. MeSH descriptor [Fruit] this term only
136. fruit*:ab,ti
137. apple*:ab,ti
138. pear*:ab,ti
139. banana*:ab,ti
140. orange*:ab,ti
141. grape*:ab,ti
142. kiwi*:ab,ti
143. citrus:ab,ti
144. grapefruit*:ab,ti
145. pulses:ab,ti
146. beans:ab,ti

147. lentil*:ab,ti
148. chickpea*:ab,ti
149. legume*:ab,ti
150. lupin*:ab,ti
151. soy:ab,ti
152. soya:ab,ti
153. nut*:ab,ti
154. almond*:ab,ti
155. peanut*:ab,ti
156. groundnut*:ab,ti
157. MeSH descriptor [Nuts] this term only
158. seed*:ab,ti
159. sesame:ab,ti
160. mustard:ab,ti
161. MeSH descriptor [Seeds] this term only
162. MeSH descriptor [Meat] explode all trees
163. meat:ab,ti
164. beef:ab,ti
165. pork:ab,ti
166. lamb:ab,ti
167. poultry:ab,ti
168. chicken:ab,ti
169. turkey:ab,ti
170. duck:ab,ti
171. fish:ab,ti
172. MeSH descriptor [Fatty Acids] this term only
173. MeSH descriptor [Fatty Acids, Omega-3] explode all trees
174. MeSH descriptor [Fatty Acids, Omega-6] explode all trees
175. omega-3:ab,ti
176. omega-6:ab,ti
177. PUFA:ab,ti
178. fat:ab,ti
179. fats:ab,ti
180. fatty:ab,ti
181. egg:ab,ti
182. eggs:ab,ti
183. MeSH descriptor [Eggs] explode all trees
184. MeSH descriptor [Bread] this term only
185. bread:ab,ti
186. oil:ab,ti
187. oils:ab,ti
188. oily:ab,ti
189. omega:ab,ti
190. MeSH descriptor [Seafood] explode all trees
191. seafood:ab,ti
192. shellfish:ab,ti
193. crustacean*:ab,ti
194. mollusc*:ab,ti
195. MeSH descriptor [Shellfish] this term only
196. MeSH descriptor [Dairy Products] this term only

197. dairy:ab,ti
198. MeSH descriptor [Milk] explode all trees
199. milk:ab,ti
200. MeSH descriptor [Infant Formula] this term only
201. formula*:ab,ti
202. hydrolysed:ab,ti
203. MeSH descriptor [Infant Food] this term only
204. yoghurt:ab,ti
205. probiotic:ab,ti
206. prebiotic*:ab,ti
207. butter:ab,ti
208. herb*:ab,ti
209. spice*:ab,ti
210. chilli*:ab,ti
211. condiment*:ab,ti
212. MeSH descriptor [Condiments] explode all trees
213. MeSH descriptor [Beverages] this term only
214. beverage*:ab,ti
215. “fluid intake”:ab,ti
216. water:ab,ti
217. drink*:ab,ti
218. MeSH descriptor [Food Preservation] explode all trees
219. pickled:ab,ti
220. bottled:ab,ti
221. canned:ab,ti
222. canning:ab,ti
223. smoked:ab,ti
224. preserved:ab,ti
225. preservatives:ab,ti
226. nitrosamine:ab,ti
227. hydrogenation:ab,ti
228. fortified:ab,ti
229. nitrates:ab,ti
230. nitrites:ab,ti
231. ferment*:ab,ti
232. processed:ab,ti
233. antioxidant*:ab,ti
234. “genetic modif*”:ab,ti
235. “genetically modif*”:ab,ti
236. MeSH descriptor [Cooking] this term only
237. cooking:ab,ti
238. cooked:ab,ti
239. grill:ab,ti
240. grilled:ab,ti
241. fried:ab,ti
242. fry:ab,ti
243. roast:ab,ti
244. bake:ab,ti
245. baked:ab,ti
246. stewing:ab,ti

247. stewed:ab,ti
248. casserol*:ab,ti
249. broil:ab,ti
250. broiled:ab,ti
251. boiled:ab,ti
252. poach:ab,ti
253. poached:ab,ti
254. steamed:ab,ti
255. barbecue*:ab,ti
256. chargrill*:ab,ti
257. salt:ab,ti
258. salting:ab,ti
259. salted:ab,ti
260. fiber:ab,ti
261. fibre:ab,ti
262. polysaccharide*:ab,ti
263. starch:ab,ti
264. starchy:ab,ti
265. carbohydrate*:ab,ti
266. lipid*:ab,ti
267. “linoleic acid*”:ab,ti
268. sugar*:ab,ti
269. sweetener*:ab,ti
270. saccharin*:ab,ti
271. aspartame:ab,ti
272. sucrose:ab,ti
273. xylitol:ab,ti
274. cholesterol:ab,ti
275. “hydrogenated lard”:ab,ti
276. “dietary protein”:ab,ti
277. “dietary proteins”:ab,ti
278. “protein intake”:ab,ti
279. “animal protein*”:ab,ti
280. “total protein*”:ab,ti
281. “vegetable protein*”:ab,ti
282. “plant protein*”:ab,ti
283. MeSH descriptor [Dietary Carbohydrates] explode all trees
284. MeSH descriptor [Dietary Fats] explode all trees
285. MeSH descriptor [Dietary Fiber] explode all trees
286. MeSH descriptor [Dietary Proteins] explode all trees
287. MeSH descriptor [Dietary Supplements] explode all trees
288. MeSH descriptor [Food Additives] explode all trees
289. MeSH descriptor [Vitamins] explode all trees
290. supplements:ab,ti
291. supplement:ab,ti
292. vitamin*:ab,ti
293. retinol:ab,ti
294. carotenoid*:ab,ti
295. tocopherol:ab,ti
296. folate*:ab,ti

297. “folic acid”:ab,ti
298. methionine:ab,ti
299. riboflavin:ab,ti
300. thiamine:ab,ti
301. niacin:ab,ti
302. pyridoxine:ab,ti
303. cobalamin:ab,ti
304. mineral*:ab,ti
305. sodium:ab,ti
306. iron:ab,ti
307. calcium:ab,ti
308. selenium:ab,ti
309. iodine:ab,ti
310. magnesium:ab,ti
311. potassium:ab,ti
312. zinc:ab,ti
313. copper:ab,ti
314. phosphorus:ab,ti
315. manganese:ab,ti
316. chromium:ab,ti
317. phytochemical:ab,ti
318. polyphenol*:ab,ti
319. phytoestrogen*:ab,ti
320. genistein:ab,ti
321. saponin*:ab,ti
322. coumarin*:ab,ti
323. flavonoid*:ab,ti
324. polyphenol*:ab,ti
325. flavonol*:ab,ti
326. flavone*:ab,ti
327. isoflavone*:ab,ti
328. catechin*:ab,ti
329. “ascorbic acid*”:ab,ti
330. “hydroxy cholecalciferol*”:ab,ti
331. hydroxycholecalciferol*:ab,ti
332. tocotrienol*:ab,ti
333. carotene*:ab,ti
334. cryptoxanthin*:ab,ti
335. lycopene*:ab,ti
336. lutein*:ab,ti
337. zeaxanthin*:ab,ti
338. selenium*:ab,ti
339. “organic diet*”:ab,ti
340. MeSH descriptor [Food, Organic] this term only
341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or

156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg*:ab,ti
343. asthma*:ab,ti
344. wheeze:ab,ti
345. wheezing:ab,ti
346. “bronchial hyperresponsiveness”:ab,ti
347. “bronchial hyperreactivity”:ab,ti
348. “Forced expiratory volume”:ab,ti
349. “FEV1”:ab,ti
350. "FEV 1":ab,ti
351. "FEV0.5":ab,ti
352. "FEV 0.5":ab,ti
353. “Forced vital capacity”:ab,ti
354. FVC:ab,ti
355. “Peak expiratory flow rate”:ab,ti
356. PEFR:ab,ti
357. eczema:ab,ti
358. neurodermatitis:ab,ti
359. rhinitis:ab,ti
360. “besniers prurigo”:ab,ti
361. rhinoconjunctivitis:ab,ti
362. hayfever:ab,ti
363. “hay fever”:ab,ti
364. poll*nosis:ab,ti
365. SAR:ab,ti
366. “pollen allergy”:ab,ti
367. conjunctivitis:ab,ti
368. immunoglobulin e:ab,ti
369. Total IgE:ab,ti
370. “autoimmune disease*”:ab,ti
371. diabetes:ab,ti
372. diabetic:ab,ti
373. “type 1”:ab,ti
374. “c*eliac disease”:ab,ti
375. “crohn* disease”:ab,ti
376. “Inflammatory Bowel Disease*”:ab,ti

377. “Ulcerative colitis”:ab,ti
378. (Lympho* NEAR/3 thyroiditi*):ab,ti
379. (Thyroiditi* NEAR/3 autoimmune):ab,ti
380. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
381. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
382. “Graves* disease”:ab,ti
383. “Basedow* disease”:ab,ti
384. “exophthalmic goiter*”:ab,ti
385. (“Still* Disease” NEAR/3 (juvenile or onset)):ab,ti
386. (Juvenile NEAR/3 arthriti*):ab,ti
387. vitiligo:ab,ti
388. Psorias*s:ab,ti
389. (Arthriti* NEAR/3 Psoria*):ab,ti
390. “atopic disease”:ab,ti
391. “atopic dermatitis”:ab,ti
392. (food* NEAR/3 sensiti*):ab,ti
393. (food* NEAR/3 toleran*):ab,ti
394. (food* NEAR/3 intoleran*):ab,ti
395. ((aero or air*) NEAR/3 allergen*):ab,ti
396. (aeroallergen* NEAR/3 sensiti*):ab,ti
397. (allergen* NEAR/3 sensiti*):ab,ti
398. “skin prick test*”:ab,ti
399. atopy:ab,ti
400. hypersensitiv*:ab,ti
401. MeSH descriptor [Hypersensitivity] this term only
402. MeSH descriptor [Food Hypersensitivity] explode all trees
403. MeSH descriptor [Respiratory Hypersensitivity] this term only
404. MeSH descriptor [Asthma] this term only
405. MeSH descriptor [Bronchial Hyperreactivity] this term only
406. MeSH descriptor [Forced Expiratory Volume] this term only
407. MeSH descriptor [Vital Capacity] this term only
408. MeSH descriptor [Peak Expiratory Flow Rate] this term only
409. MeSH descriptor [Eczema] this term only
410. MeSH descriptor [Neurodermatitis] this term only
411. MeSH descriptor [Rhinitis] this term only
412. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
413. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
414. MeSH descriptor [Conjunctivitis] this term only
415. MeSH descriptor [Immunoglobulin E] this term only
416. MeSH descriptor [Autoimmune Diseases] this term only
417. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
418. MeSH descriptor [Celiac Disease] this term only
419. MeSH descriptor [Crohn Disease] this term only
420. MeSH descriptor [Inflammatory Bowel Diseases] this term only
421. MeSH descriptor [Colitis, Ulcerative] this term only
422. MeSH descriptor [Thyroiditis, Autoimmune] this term only
423. MeSH descriptor [Hashimoto Disease] this term only
424. MeSH descriptor [Postpartum Thyroiditis] this term only
425. MeSH descriptor [Graves Disease] this term only
426. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only

427. MeSH descriptor [Vitiligo] this term only
428. MeSH descriptor [Psoriasis] this term only
429. MeSH descriptor [Arthritis, Psoriatic] this term only
430. MeSH descriptor [Dermatitis, Atopic] this term only
431. MeSH descriptor [Hypersensitivity, Immediate] this term only
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant*:ab,ti
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
436. 434 or 435
437. (old or age*):ab,ti
438. 436 and 437
439. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
440. ((first or second or two) NEAR/3 "year* of life"):ab,ti
441. MeSH descriptor [Infant] this term only
442. MeSH descriptor [Infant, Newborn] this term only
443. (maternal NEAR/7 pregnan*):ab,ti
444. (maternal NEAR/7 lactat*):ab,ti
445. (mother* NEAR/7 pregnan*):ab,ti
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. 16 or 73 or 341
448. 432 and 446 and 447
Publication date from 2011

14. Appendix 3 Search Strategies for original articles (Review C)

Medline

1. Diet/
2. Diet Therapy/
3. Nutritional Sciences/
4. Child Nutrition Sciences/
5. diet.ab,ti.
6. diets.ab,ti.
7. Diet, Mediterranean/
8. mediterranean diet$.ab,ti.
9. dietetic.ab,ti.
10. dietary.ab,ti.
11. eat.ab,ti.
12. eating.ab,ti.
13. intake.ab,ti.
14. nutrient?.ab,ti.
15. nutrition.ab,ti.
16. Diet, Vegetarian/
17. vegetarian?.ab,ti.
18. vegan$.ab,ti.
19. Diet, Macrobiotic/
20. macrobiotic?.ab,ti.
21. Food/
22. food$.ab,ti.
23. feed.ab,ti.
24. feeding.ab,ti.
25. cereal$.ab,ti.
26. grain$.ab,ti.
27. granary.ab,ti.
28. wholegrain.ab,ti.
29. wholewheat.ab,ti.
30. whole wheat.ab,ti.
31. wheat.ab,ti.
32. wheatgerm.ab,ti.
33. rye.ab,ti.
34. barley.ab,ti.
35. oat?.ab,ti.
36. exp Cereals/
37. root?.ab,ti.
38. tuber?.ab,ti.
39. exp Vegetables/
40. vegetable$.ab,ti.
41. onion$.ab,ti.
42. spinach.ab,ti.
43. chard.ab,ti.
44. tomato$.ab,ti.
45. pepper$.ab,ti.

46. carrot$.ab,ti.
47. beetroot.ab,ti.
48. asparagus.ab,ti.
49. garlic.ab,ti.
50. pumpkin.ab,ti.
51. sprouts.ab,ti.
52. broccoli.ab,ti.
53. cabbage$.ab,ti.
54. celery.ab,ti.
55. ginger.ab,ti.
56. potato$.ab,ti.
57. crisps.ab,ti.
58. fries.ab,ti.
59. syrup.ab,ti.
60. honey.ab,ti.
61. Honey/
62. Fruit/
63. fruit$.ab,ti.
64. apple?.ab,ti.
65. pear?.ab,ti.
66. banana?.ab,ti.
67. orange?.ab,ti.
68. grape?.ab,ti.
69. kiwi?.ab,ti.
70. citrus.ab,ti.
71. grapefruit?.ab,ti.
72. pulses.ab,ti.
73. beans.ab,ti.
74. lentil?.ab,ti.
75. chickpea?.ab,ti.
76. legume?.ab,ti.
77. lupin?.ab,ti.
78. soy.ab,ti.
79. soya.ab,ti.
80. nut?.ab,ti.
81. almond?.ab,ti.
82. peanut?.ab,ti.
83. groundnut?.ab,ti.
84. Nuts/
85. seed?.ab,ti.
86. sesame.ab,ti.
87. mustard.ab,ti.
88. Seeds/
89. exp Meat/
90. meat.ab,ti.
91. beef.ab,ti.
92. pork.ab,ti.
93. lamb.ab,ti.
94. poultry.ab,ti.
95. chicken.ab,ti.

96. turkey.ab,ti.
97. duck.ab,ti.
98. fish.ab,ti.
99. Fatty Acids/
100. exp Fatty Acids, Omega-3/
101. exp Fatty Acids, Omega-6/
102. omega-3.ab,ti.
103. omega-6.ab,ti.
104. PUFA.ab,ti.
105. fat.ab,ti.
106. fats.ab,ti.
107. fatty.ab,ti.
108. egg.ab,ti.
109. eggs.ab,ti.
110. exp Eggs/
111. Bread/
112. bread.ab,ti.
113. oil.ab,ti.
114. oils.ab,ti.
115. oily.ab,ti.
116. omega.ab,ti.
117. exp Seafood/
118. seafood.ab,ti.
119. shellfish.ab,ti.
120. crustacean?.ab,ti.
121. mollusc?.ab,ti.
122. Shellfish/
123. Dairy Products/
124. dairy.ab,ti.
125. exp Milk/
126. milk.ab,ti.
127. Infant Formula/
128. formula?.ab,ti.
129. hydrolysed.ab,ti.
130. Infant Food/
131. yoghurt.ab,ti.
132. probiotic.ab,ti.
133. prebiotic?.ab,ti.
134. butter.ab,ti.
135. herb?.ab,ti.
136. spice?.ab,ti.
137. chilli$.ab,ti.
138. condiment?.ab,ti.
139. exp Condiments/
140. Beverages/
141. beverage?.ab,ti.
142. fluid intake.ab,ti.
143. water.ab,ti.
144. drink$.ab,ti.
145. exp Food Preservation/

146. pickled.ab,ti.
147. bottled.ab,ti.
148. canned.ab,ti.
149. canning.ab,ti.
150. smoked.ab,ti.
151. preserved.ab,ti.
152. preservatives.ab,ti.
153. nitrosamine.ab,ti.
154. hydrogenation.ab,ti.
155. fortified.ab,ti.
156. nitrates.ab,ti.
157. nitrites.ab,ti.
158. ferment$.ab,ti.
159. processed.ab,ti.
160. antioxidant$.ab,ti.
161. genetic modif$.ab,ti.
162. genetically modif$.ab,ti.
163. Cooking/
164. cooking.ab,ti.
165. cooked.ab,ti.
166. grill.ab,ti.
167. grilled.ab,ti.
168. fried.ab,ti.
169. fry.ab,ti.
170. roast.ab,ti.
171. bake.ab,ti.
172. baked.ab,ti.
173. stewing.ab,ti.
174. stewed.ab,ti.
175. casserol$.ab,ti.
176. broil.ab,ti.
177. broiled.ab,ti.
178. boiled.ab,ti.
179. poach.ab,ti.
180. poached.ab,ti.
181. steamed.ab,ti.
182. barbecue$.ab,ti.
183. chargrill$.ab,ti.
184. salt.ab,ti.
185. salting.ab,ti.
186. salted.ab,ti.
187. fiber.ab,ti.
188. fibre.ab,ti.
189. polysaccharide$.ab,ti.
190. starch.ab,ti.
191. starchy.ab,ti.
192. carbohydrate$.ab,ti.
193. lipid$.ab,ti.
194. linoleic acid$.ab,ti.
195. sugar$.ab,ti.

196. sweetener$.ab,ti.
197. saccharin$.ab,ti.
198. aspartame.ab,ti.
199. sucrose.ab,ti.
200. xylitol.ab,ti.
201. cholesterol.ab,ti.
202. hydrogenated lard.ab,ti.
203. dietary protein.ab,ti.
204. dietary proteins.ab,ti.
205. protein intake.ab,ti.
206. animal protein$.ab,ti.
207. total protein$.ab,ti.
208. vegetable protein$.ab,ti.
209. plant protein$.ab,ti.
210. exp Dietary Carbohydrates/
211. exp Dietary Fats/
212. exp Dietary Fiber/
213. exp Dietary Proteins/
214. exp Dietary Supplements/
215. exp Food Additives/
216. exp Vitamins/
217. supplements.ab,ti.
218. supplement.ab,ti.
219. vitamin$.ab,ti.
220. retinol.ab,ti.
221. carotenoid$.ab,ti.
222. tocopherol.ab,ti.
223. folate$.ab,ti.
224. folic acid.ab,ti.
225. methionine.ab,ti.
226. riboflavin.ab,ti.
227. thiamine.ab,ti.
228. niacin.ab,ti.
229. pyridoxine.ab,ti.
230. cobalamin.ab,ti.
231. mineral$.ab,ti.
232. sodium.ab,ti.
233. iron.ab,ti.
234. calcium.ab,ti.
235. selenium.ab,ti.
236. iodine.ab,ti.
237. magnesium.ab,ti.
238. potassium.ab,ti.
239. zinc.ab,ti.
240. copper.ab,ti.
241. phosphorus.ab,ti.
242. manganese.ab,ti.
243. chromium.ab,ti.
244. phytochemical.ab,ti.
245. polyphenol$.ab,ti.

246. phytoestrogen$.ab,ti.
247. genistein.ab,ti.
248. saponin$.ab,ti.
249. coumarin$.ab,ti.
250. flavonoid$.ab,ti.
251. polyphenol$.ab,ti.
252. flavonol$.ab,ti.
253. flavone$.ab,ti.
254. isoflavone$.ab,ti.
255. catechin$.ab,ti.
256. ascorbic acid$.ab,ti.
257. hydroxy cholecalciferol$.ab,ti.
258. hydroxycholecalciferol$.ab,ti.
259. tocotrienol$.ab,ti.
260. carotene$.ab,ti.
261. cryptoxanthin$.ab,ti.
262. lycopene$.ab,ti.
263. lutein$.ab,ti.
264. zeaxanthin$.ab,ti.
265. selenium$.ab,ti.
266. organic diet?.ab,ti.
267. Food, Organic/
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg$.ab,ti.
270. asthma$.ab,ti.
271. wheeze.ab,ti.
272. wheezing.ab,ti.
273. bronchial hyperresponsiveness.ab,ti.
274. bronchial hyperreactivity.ab,ti.
275. Forced expiratory volume.ab,ti.
276. FEV1.ab,ti.
277. "FEV 1".ab,ti.

278. "FEV0.5".ab,ti.
279. "FEV 0.5".ab,ti.
280. Forced vital capacity.ab,ti.
281. FVC.ab,ti.
282. Peak expiratory flow rate.ab,ti.
283. PEFR.ab,ti.
284. eczema.ab,ti.
285. neurodermatitis.ab,ti.
286. rhinitis.ab,ti.
287. besniers prurigo.ab,ti.
288. rhinoconjunctivitis.ab,ti.
289. hayfever.ab,ti.
290. (hay adj fever).ab,ti.
291. poll?nosis.ab,ti.
292. SAR.ab,ti.
293. (pollen adj allergy).ab,ti.
294. conjunctivitis.ab,ti.
295. immunoglobulin e.ab,ti.
296. Total IgE.ab,ti.
297. autoimmune disease?.ab,ti.
298. diabetes.ab,ti.
299. diabetic.ab,ti.
300. type 1.ab,ti.
301. c?eliac disease.ab,ti.
302. crohn$ disease.ab,ti.
303. Inflammatory Bowel Disease?.ab,ti.
304. Ulcerative colitis.ab,ti.
305. (Lympho$ adj3 thyroiditi$).ab,ti.
306. (Thyroiditi$ adj3 autoimmune).ab,ti.
307. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
308. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
309. Graves? disease.ab,ti.
310. Basedow$ disease.ab,ti.
311. exophthalmic goiter?.ab,ti.
312. (Still? Disease adj3 (juvenile or onset)).ab,ti.
313. (Juvenile adj3 arthriti$).ab,ti.
314. vitiligo.ab,ti.
315. Psorias?s.ab,ti.
316. (Arthriti? adj3 Psoria$).ab,ti.
317. atopic disease.ab,ti.
318. atopic dermatitis.ab,ti.
319. (food? adj3 sensiti$).ab,ti.
320. (food? adj3 toleran$).ab,ti.
321. (food? adj3 intoleran$).ab,ti.
322. ((aero or air$) adj3 allergen?).ab,ti.
323. (aeroallergen? adj3 sensiti$).ab,ti.
324. (allergen? adj3 sensiti$).ab,ti.
325. skin prick test$.ab,ti.
326. atopy.ab,ti.
327. hypersensitiv$.ab,ti.

328. Hypersensitivity/
329. exp Food Hypersensitivity/
330. Respiratory Hypersensitivity/
331. Asthma/
332. Bronchial Hyperreactivity/
333. Forced Expiratory Volume/
334. Vital Capacity/
335. Peak Expiratory Flow Rate/
336. Eczema/
337. Neurodermatitis/
338. Rhinitis/
339. Rhinitis, Allergic, Perennial/
340. Rhinitis, Allergic, Seasonal/
341. Conjunctivitis/
342. Immunoglobulin E/
343. Autoimmune Diseases/
344. Diabetes Mellitus, Type 1/
345. Celiac Disease/
346. Crohn Disease/
347. Inflammatory Bowel Diseases/
348. Colitis, Ulcerative/
349. Thyroiditis, Autoimmune/
350. Hashimoto Disease/
351. Postpartum Thyroiditis/
352. Graves Disease/
353. Arthritis, Juvenile Rheumatoid/
354. Vitiligo/
355. Psoriasis/
356. Arthritis, Psoriatic/
357. Dermatitis, Atopic/
358. Hypersensitivity, Immediate/
359. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358
360. infant?.ab,ti.
361. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
362. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
363. 361 or 362
364. (old or age?).ab,ti.
365. 363 and 364
366. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.

367. ((first or second or two) adj3 "year? of life").ab,ti.
368. Infant/
369. Infant, Newborn/
370. (maternal adj7 pregnan$).ab,ti.
371. (maternal adj7 lactat$).ab,ti.
372. (mother? adj7 pregnan$).ab,ti.
373. 360 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372
374. clinical trial?.mp.
375. random$.mp.
376. factorial$.mp.
377. crossover$.mp.
378. placebo$.mp.
379. (doubl$ adj blind$).mp.
380. (singl$ adj blind$).mp.
381. assign$.mp.
382. volunteer$.mp.
383. cohort stud$.mp.
384. longitudinal$.mp.
385. follow-up.mp.
386. prospectiv$.mp.
387. retrospectiv$.mp.
388. case control.mp.
389. case referent.mp.
390. exp clinical trial/
391. Cross-Over Studies/
392. Placebos/
393. Double-Blind Method/
394. Single-Blind Method/
395. exp Cohort Studies/
396. case-control studies/
397. 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396
398. 268 and 359 and 373 and 397

Embase

1. diet/
2. diet therapy/
3. nutritional science/
4. diet.ti,ab.
5. diets.ti,ab.
6. Mediterranean diet/
7. mediterranean diet$.ab,ti.
8. dietetic.ab,ti.
9. dietary.ab,ti.
10. eat.ab,ti.
11. eating.ab,ti.
12. intake.ab,ti.
13. nutrient?.ab,ti.
14. nutrition.ab,ti.
15. vegetarian diet/
16. vegetarian?.ti,ab.
17. vegan$.ti,ab.
18. macrobiotic diet/
19. macrobiotic?.ti,ab.
20. food/
21. food$.ab,ti.
22. feed.ab,ti.
23. feeding.ab,ti.
24. cereal$.ab,ti.
25. grain$.ab,ti.
26. granary.ab,ti.
27. wholegrain.ab,ti.
28. wholewheat.ab,ti.
29. whole wheat.ab,ti.
30. wheat.ab,ti.
31. wheatgerm.ab,ti.
32. rye.ab,ti.
33. barley.ab,ti.
34. oat?.ab,ti.
35. exp cereal/
36. root?.ti,ab.
37. tuber?.ti,ab.
38. exp vegetable/
39. vegetable$.ab,ti.
40. onion$.ab,ti.
41. spinach.ab,ti.
42. chard.ab,ti.
43. tomato$.ab,ti.
44. pepper$.ab,ti.
45. carrot$.ab,ti.
46. beetroot.ab,ti.
47. asparagus.ab,ti.
48. garlic.ab,ti.

49. pumpkin.ab,ti.
50. sprouts.ab,ti.
51. broccoli.ab,ti.
52. cabbage$.ab,ti.
53. celery.ab,ti.
54. ginger.ab,ti.
55. potato$.ab,ti.
56. crisps.ab,ti.
57. fries.ab,ti.
58. syrup.ab,ti.
59. honey.ab,ti.
60. honey/
61. fruit/
62. fruit$.ab,ti.
63. apple?.ab,ti.
64. pear?.ab,ti.
65. banana?.ab,ti.
66. orange?.ab,ti.
67. grape?.ab,ti.
68. kiwi?.ab,ti.
69. citrus.ab,ti.
70. grapefruit?.ab,ti.
71. pulses.ab,ti.
72. beans.ab,ti.
73. lentil?.ab,ti.
74. chickpea?.ab,ti.
75. legume?.ab,ti.
76. lupin?.ab,ti.
77. soy.ab,ti.
78. soya.ab,ti.
79. nut?.ab,ti.
80. almond?.ab,ti.
81. peanut?.ab,ti.
82. groundnut?.ab,ti.
83. exp nut/
84. seed?.ti,ab.
85. sesame.ti,ab.
86. mustard.ti,ab.
87. plant seed/
88. meat/
89. meat.ab,ti.
90. beef.ab,ti.
91. pork.ab,ti.
92. lamb.ab,ti.
93. poultry.ab,ti.
94. chicken.ab,ti.
95. turkey.ab,ti.
96. duck.ab,ti.
97. fish.ab,ti.
98. fatty acid/

99. omega 3 fatty acid/
100. omega 6 fatty acid/
101. omega-3.ab,ti.
102. omega-6.ab,ti.
103. PUFA.ab,ti.
104. fat.ab,ti.
105. fats.ab,ti.
106. fatty.ab,ti.
107. egg.ab,ti.
108. eggs.ab,ti.
109. exp egg/
110. bread/
111. bread.ti,ab.
112. oil.ti,ab.
113. oils.ti,ab.
114. oily.ti,ab.
115. omega.ti,ab.
116. sea food/
117. seafood.ti,ab.
118. shellfish.ti,ab.
119. crustacean?.ti,ab.
120. mollusc?.ti,ab.
121. shellfish/
122. exp dairy product/
123. dairy.ti,ab.
124. milk/
125. milk.ti,ab.
126. artificial milk/
127. formula?.ti,ab.
128. hydrolysed.ti,ab.
129. baby food/
130. yoghurt.ab,ti.
131. probiotic.ab,ti.
132. prebiotic?.ab,ti.
133. butter.ab,ti.
134. herb?.ab,ti.
135. spice?.ab,ti.
136. chilli$.ab,ti.
137. condiment?.ab,ti.
138. exp condiment/
139. beverage/
140. beverage?.ti,ab.
141. fluid intake.ti,ab.
142. water.ti,ab.
143. drink$.ti,ab.
144. exp food preservation/
145. pickled.ab,ti.
146. bottled.ab,ti.
147. canned.ab,ti.
148. canning.ab,ti.

149. smoked.ab,ti.
150. preserved.ab,ti.
151. preservatives.ab,ti.
152. nitrosamine.ab,ti.
153. hydrogenation.ab,ti.
154. fortified.ab,ti.
155. nitrates.ab,ti.
156. nitrites.ab,ti.
157. ferment$.ab,ti.
158. processed.ab,ti.
159. antioxidant$.ab,ti.
160. genetic modif$.ab,ti.
161. genetically modif$.ab,ti.
162. cooking/
163. cooking.ab,ti.
164. cooked.ab,ti.
165. grill.ab,ti.
166. grilled.ab,ti.
167. fried.ab,ti.
168. fry.ab,ti.
169. roast.ab,ti.
170. bake.ab,ti.
171. baked.ab,ti.
172. stewing.ab,ti.
173. stewed.ab,ti.
174. casserol$.ab,ti.
175. broil.ab,ti.
176. broiled.ab,ti.
177. boiled.ab,ti.
178. poach.ab,ti.
179. poached.ab,ti.
180. steamed.ab,ti.
181. barbecue$.ab,ti.
182. chargrill$.ab,ti.
183. salt.ab,ti.
184. salting.ab,ti.
185. salted.ab,ti.
186. fiber.ab,ti.
187. fibre.ab,ti.
188. polysaccharide$.ab,ti.
189. starch.ab,ti.
190. starchy.ab,ti.
191. carbohydrate$.ab,ti.
192. lipid$.ab,ti.
193. linoleic acid$.ab,ti.
194. sugar$.ab,ti.
195. sweetener$.ab,ti.
196. saccharin$.ab,ti.
197. aspartame.ab,ti.
198. sucrose.ab,ti.

199. xylitol.ab,ti.
200. cholesterol.ab,ti.
201. hydrogenated lard.ab,ti.
202. dietary protein.ab,ti.
203. dietary proteins.ab,ti.
204. protein intake.ab,ti.
205. animal protein$.ab,ti.
206. total protein$.ab,ti.
207. vegetable protein$.ab,ti.
208. plant protein$.ab,ti.
209. carbohydrate diet/
210. carbohydrate intake/
211. fat intake/
212. dietary fiber/
213. protein intake/
214. diet supplementation/
215. food additive/
216. exp vitamin/
217. supplements.ab,ti.
218. supplement.ab,ti.
219. vitamin$.ab,ti.
220. retinol.ab,ti.
221. carotenoid$.ab,ti.
222. tocopherol.ab,ti.
223. folate$.ab,ti.
224. folic acid.ab,ti.
225. methionine.ab,ti.
226. riboflavin.ab,ti.
227. thiamine.ab,ti.
228. niacin.ab,ti.
229. pyridoxine.ab,ti.
230. cobalamin.ab,ti.
231. mineral$.ab,ti.
232. sodium.ab,ti.
233. iron.ab,ti.
234. calcium.ab,ti.
235. selenium.ab,ti.
236. iodine.ab,ti.
237. magnesium.ab,ti.
238. potassium.ab,ti.
239. zinc.ab,ti.
240. copper.ab,ti.
241. phosphorus.ab,ti.
242. manganese.ab,ti.
243. chromium.ab,ti.
244. phytochemical.ab,ti.
245. polyphenol$.ab,ti.
246. phytoestrogen$.ab,ti.
247. genistein.ab,ti.
248. saponin$.ab,ti.

249. coumarin$.ab,ti.
250. flavonoid$.ab,ti.
251. polyphenol$.ab,ti.
252. flavonol$.ab,ti.
253. flavone$.ab,ti.
254. isoflavone$.ab,ti.
255. catechin$.ab,ti.
256. ascorbic acid$.ab,ti.
257. hydroxy cholecalciferol$.ab,ti.
258. hydroxycholecalciferol$.ab,ti.
259. tocotrienol$.ab,ti.
260. carotene$.ab,ti.
261. cryptoxanthin$.ab,ti.
262. lycopene$.ab,ti.
263. lutein$.ab,ti.
264. zeaxanthin$.ab,ti.
265. selenium$.ab,ti.
266. organic diet?.ab,ti.
267. organic food/
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg$.ab,ti.
270. asthma$.ab,ti.
271. wheeze.ab,ti.
272. wheezing.ab,ti.
273. bronchial hyperresponsiveness.ab,ti.
274. bronchial hyperreactivity.ab,ti.
275. Forced expiratory volume.ab,ti.
276. FEV1.ab,ti.
277. "FEV 1".ab,ti.
278. "FEV0.5".ab,ti.
279. "FEV 0.5".ab,ti.
280. Forced vital capacity.ab,ti.

281. FVC.ab,ti.
282. Peak expiratory flow rate.ab,ti.
283. PEFR.ab,ti.
284. eczema.ab,ti.
285. neurodermatitis.ab,ti.
286. rhinitis.ab,ti.
287. besniers prurigo.ab,ti.
288. rhinoconjunctivitis.ab,ti.
289. hayfever.ab,ti.
290. (hay adj fever).ab,ti.
291. poll?nosis.ab,ti.
292. SAR.ab,ti.
293. (pollen adj allergy).ab,ti.
294. conjunctivitis.ab,ti.
295. immunoglobulin e.ab,ti.
296. Total IgE.ab,ti.
297. autoimmune disease?.ab,ti.
298. diabetes.ab,ti.
299. diabetic.ab,ti.
300. type 1.ab,ti.
301. c?eliac disease.ab,ti.
302. crohn$ disease.ab,ti.
303. Inflammatory Bowel Disease?.ab,ti.
304. Ulcerative colitis.ab,ti.
305. (Lympho$ adj3 thyroiditi$).ab,ti.
306. (Thyroiditi$ adj3 autoimmune).ab,ti.
307. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
308. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
309. Graves? disease.ab,ti.
310. Basedow$ disease.ab,ti.
311. exophthalmic goiter?.ab,ti.
312. (Still? Disease adj3 (juvenile or onset)).ab,ti.
313. (Juvenile adj3 arthriti$).ab,ti.
314. vitiligo.ab,ti.
315. Psorias?s.ab,ti.
316. (Arthriti? adj3 Psoria$).ab,ti.
317. atopic disease.ab,ti.
318. atopic dermatitis.ab,ti.
319. (food? adj3 sensiti$).ab,ti.
320. (food? adj3 toleran$).ab,ti.
321. (food? adj3 intoleran$).ab,ti.
322. ((aero or air$) adj3 allergen?).ab,ti.
323. (aeroallergen? adj3 sensiti$).ab,ti.
324. (allergen? adj3 sensiti$).ab,ti.
325. skin prick test$.ab,ti.
326. atopy.ab,ti.
327. hypersensitiv$.ab,ti.
328. exp hypersensitivity/
329. respiratory tract allergy/
330. asthma/

331. wheezing/
332. bronchus hyperreactivity/
333. forced expiratory volume/
334. forced vital capacity/
335. peak expiratory flow/
336. eczema/
337. neurodermatitis/
338. rhinitis/
339. rhinoconjunctivitis/
340. hay fever/
341. pollen allergy/
342. perennial rhinitis/
343. conjunctivitis/
344. immunoglobulin E/
345. autoimmune disease/
346. diabetes mellitus/
347. insulin dependent diabetes mellitus/
348. celiac disease/
349. Crohn disease/
350. enteritis/
351. ulcerative colitis/
352. autoimmune thyroiditis/
353. Hashimoto disease/
354. postpartum thyroiditis/
355. Graves disease/
356. juvenile rheumatoid arthritis/
357. vitiligo/
358. psoriasis/
359. psoriatic arthritis/
360. atopic dermatitis/
361. nutritional intolerance/
362. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361
363. infant?.ab,ti.
364. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
365. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
366. 364 or 365
367. (old or age?).ab,ti.
368. 366 and 367

369. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
370. ((first or second or two) adj3 "year? of life").ab,ti.
371. infant/
372. newborn/
373. (maternal adj7 pregnan$).ti,ab.
374. (maternal adj7 lactat$).ti,ab.
375. (mother? adj7 pregnan$).ti,ab.
376. 363 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375
377. clinical trial?.mp.
378. random$.mp.
379. factorial$.mp.
380. crossover$.mp.
381. placebo$.mp.
382. (doubl$ adj blind$).mp.
383. (singl$ adj blind$).mp.
384. assign$.mp.
385. volunteer$.mp.
386. cohort stud$.mp.
387. longitudinal$.mp.
388. follow-up.mp.
389. prospectiv$.mp.
390. retrospectiv$.mp.
391. case control.mp.
392. case referent.mp.
393. exp clinical trial/
394. crossover procedure/
395. placebo/
396. double blind procedure/
397. single blind procedure/
398. cohort analysis/
399. longitudinal study/
400. follow up/
401. prospective study/
402. retrospective study/
403. exp case control study/
404. 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403
405. 268 and 362 and 376 and 404

2.3. LILACS

(tw:((breast feeding) or breastfeeding or (breast fed) or breastfed or formula* or hydrolysed or bottlefed or (bottle fed) or (bottle feed*) or wean*)
AND
(tw:(allerg* or asthma* or wheez* or (bronchial hyperresponsiveness) or (bronchial hyperreactivity) or (Forced expiratory volume) or FEV1 or (FEV 1) or FEV0.5 or (FEV 0.5) or (Forced vital capacity) or FVC or (Peak expiratory flow rate) or PEFR or eczema or neurodermatitis or rhinitis or (besniers prurigo) or rhinoconjunctivitis or hayfever or (hay fever) or poll?nosis or SAR or (pollen allergy) or conjunctivitis or (immunoglobulin e) or (Total IgE) or (autoimmune disease*) or diabetes or diabetic or (type 1) or (c?eliac disease) or (crohn* disease) or (Inflammatory Bowel Disease*) or (Ulcerative colitis) or (Lympho* thyroiditi*) or (Thyroiditi* autoimmune) or (Hashimoto* syndrome*) or (Hashimoto* thyroiditis*) or (Hashimoto* disease*) or (Thyroiditi* post-partum) or (Thyroiditi* postpartum) or (Graves* Disease) or (Basedow* disease) or (exophthalmic goiter*) or (Still's Disease) or (Stills disease) or (Juvenile arthriti*) or vitiligo or Psorias?s or (Arthriti* Psoria*) or (atopic disease) or (atopic dermatitis) or (food* sensiti*) or (food* toleran*) or (food* intoleran*) or (aero allergen*) or (air* allergen*) or (aeroallergen* sensiti*) or (allergen* sensiti*) or (skin prick test*) or atopy or hypersensitive*)
AND
db:("LILACS")
AND
type_of_study:("clinical_trials" or "case_control" or "cohort" or "systematic_reviews")
AND
limit:("infant" or "newborn" or "preschool" or "child")

COCHRANE Library

1. MeSH descriptor: [Diet] this term only
2. MeSH descriptor: [Diet Therapy] this term only
3. MeSH descriptor: [Nutritional Sciences] this term only
4. MeSH descriptor: [Child Nutrition Sciences] this term only
5. diet:ab,ti
6. diets:ab,ti
7. MeSH descriptor: [Diet, Mediterranean] this term only
8. “mediterranean diet*”:ab,ti
9. dietetic:ab,ti
10. dietary:ab,ti
11. eat:ab,ti
12. eating:ab,ti
13. intake:ab,ti
14. nutrient*:ab,ti
15. nutrition:ab,ti
16. MeSH descriptor: [Diet, Vegetarian] this term only
17. vegetarian*:ab,ti
18. vegan*:ab,ti
19. MeSH descriptor: [Diet, Macrobiotic] this term only
20. macrobiotic*:ab,ti
21. MeSH descriptor: [Food] this term only
22. food*:ab,ti
23. feed:ab,ti
24. feeding:ab,ti
25. cereal*:ab,ti
26. grain*:ab,ti
27. granary:ab,ti
28. wholegrain:ab,ti
29. wholewheat:ab,ti
30. “whole wheat”:ab,ti
31. wheat:ab,ti
32. wheatgerm:ab,ti
33. rye:ab,ti
34. barley:ab,ti
35. oat*:ab,ti
36. MeSH descriptor: [Cereals] explode all trees
37. root*:ab,ti
38. tuber*:ab,ti
39. MeSH descriptor: [Vegetables] explode all trees
40. vegetable*:ab,ti
41. onion*:ab,ti
42. spinach:ab,ti
43. chard:ab,ti
44. tomato*:ab,ti
45. pepper*:ab,ti
46. carrot*:ab,ti
47. beetroot:ab,ti
48. asparagus:ab,ti
49. garlic:ab,ti

50. pumpkin:ab,ti
51. sprouts:ab,ti
52. broccoli:ab,ti
53. cabbage*:ab,ti
54. celery:ab,ti
55. ginger:ab,ti
56. potato*:ab,ti
57. crisps:ab,ti
58. fries:ab,ti
59. syrup:ab,ti
60. honey:ab,ti
61. MeSH descriptor: [Honey] this term only
62. MeSH descriptor: [Fruit] this term only
63. fruit*:ab,ti
64. apple*:ab,ti
65. pear*:ab,ti
66. banana*:ab,ti
67. orange*:ab,ti
68. grape*:ab,ti
69. kiwi*:ab,ti
70. citrus:ab,ti
71. grapefruit*:ab,ti
72. pulses:ab,ti
73. beans:ab,ti
74. lentil*:ab,ti
75. chickpea*:ab,ti
76. legume*:ab,ti
77. lupin*:ab,ti
78. soy:ab,ti
79. soya:ab,ti
80. nut*:ab,ti
81. almond*:ab,ti
82. peanut*:ab,ti
83. groundnut*:ab,ti
84. MeSH descriptor: [Nuts] this term only
85. seed*:ab,ti
86. sesame:ab,ti
87. mustard:ab,ti
88. MeSH descriptor: [Seeds] this term only
89. MeSH descriptor: [Meat] explode all trees
90. meat:ab,ti
91. beef:ab,ti
92. pork:ab,ti
93. lamb:ab,ti
94. poultry:ab,ti
95. chicken:ab,ti
96. turkey:ab,ti
97. duck:ab,ti
98. fish:ab,ti
99. MeSH descriptor: [Fatty Acids] this term only

100. MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
101. MeSH descriptor: [Fatty Acids, Omega-6] explode all trees
102. omega-3:ab,ti
103. omega-6:ab,ti
104. PUFA:ab,ti
105. fat:ab,ti
106. fats:ab,ti
107. fatty:ab,ti
108. egg:ab,ti
109. eggs:ab,ti
110. MeSH descriptor: [Eggs] explode all trees
111. MeSH descriptor: [Bread] this term only
112. bread:ab,ti
113. oil:ab,ti
114. oils:ab,ti
115. oily:ab,ti
116. omega:ab,ti
117. MeSH descriptor: [Seafood] explode all trees
118. seafood:ab,ti
119. shellfish:ab,ti
120. crustacean*:ab,ti
121. mollusc*:ab,ti
122. MeSH descriptor: [Shellfish] this term only
123. MeSH descriptor: [Dairy Products] this term only
124. dairy:ab,ti
125. MeSH descriptor: [Milk] explode all trees
126. milk:ab,ti
127. MeSH descriptor: [Infant Formula] this term only
128. formula*:ab,ti
129. hydrolysed:ab,ti
130. MeSH descriptor: [Infant Food] this term only
131. yoghurt:ab,ti
132. probiotic:ab,ti
133. prebiotic*:ab,ti
134. butter:ab,ti
135. herb*:ab,ti
136. spice*:ab,ti
137. chilli*:ab,ti
138. condiment*:ab,ti
139. MeSH descriptor: [Condiments] explode all trees
140. MeSH descriptor: [Beverages] this term only
141. beverage*:ab,ti
142. “fluid intake”:ab,ti
143. water:ab,ti
144. drink*:ab,ti
145. MeSH descriptor: [Food Preservation] explode all trees
146. pickled:ab,ti
147. bottled:ab,ti
148. canned:ab,ti
149. canning:ab,ti

150. smoked:ab,ti
151. preserved:ab,ti
152. preservatives:ab,ti
153. nitrosamine:ab,ti
154. hydrogenation:ab,ti
155. fortified:ab,ti
156. nitrates:ab,ti
157. nitrites:ab,ti
158. ferment*:ab,ti
159. processed:ab,ti
160. antioxidant*:ab,ti
161. “genetic modif*”:ab,ti
162. “genetically modif*”:ab,ti
163. MeSH descriptor: [Cooking] this term only
164. cooking:ab,ti
165. cooked:ab,ti
166. grill:ab,ti
167. grilled:ab,ti
168. fried:ab,ti
169. fry:ab,ti
170. roast:ab,ti
171. bake:ab,ti
172. baked:ab,ti
173. stewing:ab,ti
174. stewed:ab,ti
175. casserol*:ab,ti
176. broil:ab,ti
177. broiled:ab,ti
178. boiled:ab,ti
179. poach:ab,ti
180. poached:ab,ti
181. steamed:ab,ti
182. barbecue*:ab,ti
183. chargrill*:ab,ti
184. salt:ab,ti
185. salting:ab,ti
186. salted:ab,ti
187. fiber:ab,ti
188. fibre:ab,ti
189. polysaccharide*:ab,ti
190. starch:ab,ti
191. starchy:ab,ti
192. carbohydrate*:ab,ti
193. lipid*:ab,ti
194. “linoleic acid*”:ab,ti
195. sugar*:ab,ti
196. sweetener*:ab,ti
197. saccharin*:ab,ti
198. aspartame:ab,ti
199. sucrose:ab,ti

200. xylitol:ab,ti
201. cholesterol:ab,ti
202. “hydrogenated lard”:ab,ti
203. “dietary protein”:ab,ti
204. “dietary proteins”:ab,ti
205. “protein intake”:ab,ti
206. “animal protein*”:ab,ti
207. “total protein*”:ab,ti
208. “vegetable protein*”:ab,ti
209. “plant protein*”:ab,ti
210. MeSH descriptor: [Dietary Carbohydrates] explode all trees
211. MeSH descriptor: [Dietary Fats] explode all trees
212. MeSH descriptor: [Dietary Fiber] explode all trees
213. MeSH descriptor: [Dietary Proteins] explode all trees
214. MeSH descriptor: [Dietary Supplements] explode all trees
215. MeSH descriptor: [Food Additives] explode all trees
216. MeSH descriptor: [Vitamins] explode all trees
217. supplements:ab,ti
218. supplement:ab,ti
219. vitamin*:ab,ti
220. retinol:ab,ti
221. carotenoid*:ab,ti
222. tocopherol:ab,ti
223. folate*:ab,ti
224. “folic acid”:ab,ti
225. methionine:ab,ti
226. riboflavin:ab,ti
227. thiamine:ab,ti
228. niacin:ab,ti
229. pyridoxine:ab,ti
230. cobalamin:ab,ti
231. mineral*:ab,ti
232. sodium:ab,ti
233. iron:ab,ti
234. calcium:ab,ti
235. selenium:ab,ti
236. iodine:ab,ti
237. magnesium:ab,ti
238. potassium:ab,ti
239. zinc:ab,ti
240. copper:ab,ti
241. phosphorus:ab,ti
242. manganese:ab,ti
243. chromium:ab,ti
244. phytochemical:ab,ti
245. polyphenol*:ab,ti
246. phytoestrogen*:ab,ti
247. genistein:ab,ti
248. saponin*:ab,ti
249. coumarin*:ab,ti

250. flavonoid*:ab,ti
251. polyphenol*:ab,ti
252. flavonol*:ab,ti
253. flavone*:ab,ti
254. isoflavone*:ab,ti
255. catechin*:ab,ti
256. “ascorbic acid*”:ab,ti
257. “hydroxy cholecalciferol*”:ab,ti
258. hydroxycholecalciferol*:ab,ti
259. tocotrienol*:ab,ti
260. carotene*:ab,ti
261. cryptoxanthin*:ab,ti
262. lycopene*:ab,ti
263. lutein*:ab,ti
264. zeaxanthin*:ab,ti
265. selenium*:ab,ti
266. “organic diet*”:ab,ti
267. MeSH descriptor: [Food, Organic] this term only
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg*:ab,ti
270. asthma*:ab,ti
271. wheeze:ab,ti
272. wheezing:ab,ti
273. “bronchial hyperresponsiveness”:ab,ti
274. “bronchial hyperreactivity”:ab,ti
275. “Forced expiratory volume”:ab,ti
276. “FEV1”:ab,ti
277. "FEV 1":ab,ti
278. "FEV0.5":ab,ti
279. "FEV 0.5":ab,ti
280. “Forced vital capacity”:ab,ti
281. FVC:ab,ti

282. “Peak expiratory flow rate”:ab,ti
283. PEFR:ab,ti
284. eczema:ab,ti
285. neurodermatitis:ab,ti
286. rhinitis:ab,ti
287. “besniers prurigo”:ab,ti
288. rhinoconjunctivitis:ab,ti
289. hayfever:ab,ti
290. “hay fever”:ab,ti
291. poll*nosis:ab,ti
292. SAR:ab,ti
293. “pollen allergy”:ab,ti
294. conjunctivitis:ab,ti
295. “immunoglobulin e”:ab,ti
296. “Total IgE”:ab,ti
297. “autoimmune disease*”:ab,ti
298. diabetes:ab,ti
299. diabetic:ab,ti
300. “type 1”:ab,ti
301. “c*eliac disease”:ab,ti
302. “crohn* disease”:ab,ti
303. “Inflammatory Bowel Disease*”:ab,ti
304. “Ulcerative colitis”:ab,ti
305. (Lympho* NEAR/3 thyroiditi*):ab,ti
306. (Thyroiditi* NEAR/3 autoimmune):ab,ti
307. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
308. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
309. “Graves* disease”:ab,ti
310. “Basedow* disease”:ab,ti
311. “exophthalmic goiter*”:ab,ti
312. (Still* Disease NEAR/3 (juvenile or onset)):ab,ti
313. (Juvenile NEAR/3 arthriti*):ab,ti
314. vitiligo:ab,ti
315. Psorias*s:ab,ti
316. (Arthriti* NEAR/3 Psoria*):ab,ti
317. “atopic disease”:ab,ti
318. “atopic dermatitis”:ab,ti
319. (food* NEAR/3 sensiti*):ab,ti
320. (food* NEAR/3 toleran*):ab,ti
321. (food* NEAR/3 intoleran*):ab,ti
322. ((aero or air*) NEAR/3 allergen*):ab,ti
323. (aeroallergen* NEAR/3 sensiti*):ab,ti
324. (allergen* NEAR/3 sensiti*):ab,ti
325. “skin prick test*”:ab,ti
326. atopy:ab,ti
327. hypersensitiv*:ab,ti
328. MeSH descriptor: [Hypersensitivity] this term only
329. MeSH descriptor: [Food Hypersensitivity] explode all trees
330. MeSH descriptor: [Respiratory Hypersensitivity] this term only
331. MeSH descriptor: [Asthma] this term only

332. MeSH descriptor: [Bronchial Hyperreactivity] this term only
333. MeSH descriptor: [Forced Expiratory Volume] this term only
334. MeSH descriptor: [Vital Capacity] this term only
335. MeSH descriptor: [Peak Expiratory Flow Rate] this term only
336. MeSH descriptor: [Eczema] this term only
337. MeSH descriptor: [Neurodermatitis] this term only
338. MeSH descriptor: [Rhinitis] this term only
339. MeSH descriptor: [Rhinitis, Allergic, Perennial] this term only
340. MeSH descriptor: [Rhinitis, Allergic, Seasonal] this term only
341. MeSH descriptor: [Conjunctivitis] this term only
342. MeSH descriptor: [Immunoglobulin E] this term only
343. MeSH descriptor: [Autoimmune Diseases] this term only
344. MeSH descriptor: [Diabetes Mellitus, Type 1] this term only
345. MeSH descriptor: [Celiac Disease] this term only
346. MeSH descriptor: [Crohn Disease] this term only
347. MeSH descriptor: [Inflammatory Bowel Diseases] this term only
348. MeSH descriptor: [Colitis, Ulcerative] this term only
349. MeSH descriptor: [Thyroiditis, Autoimmune] this term only
350. MeSH descriptor: [Hashimoto Disease] this term only
351. MeSH descriptor: [Postpartum Thyroiditis] this term only
352. MeSH descriptor: [Graves Disease] this term only
353. MeSH descriptor: [Arthritis, Juvenile Rheumatoid] this term only
354. MeSH descriptor: [Vitiligo] this term only
355. MeSH descriptor: [Psoriasis] this term only
356. MeSH descriptor: [Arthritis, Psoriatic] this term only
357. MeSH descriptor: [Dermatitis, Atopic] this term only
358. MeSH descriptor: [Hypersensitivity, Immediate] this term only
359. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358
360. infant*:ab,ti
361. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
362. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
363. 361 or 362
364. (old or age*):ab,ti
365. 363 and 364
366. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
367. ((first or second or two) NEAR/3 "year* of life"):ab,ti
368. MeSH descriptor: [Infant] this term only
369. MeSH descriptor: [Infant, Newborn] this term only

370. (maternal NEAR/7 pregnan*):ab,ti
371. (maternal NEAR/7 lactat*):ab,ti
372. (mother* NEAR/7 pregnan*):ab,ti
373. 360 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372
374. “clinical trial*”
375. random*
376. factorial*
377. crossover*
378. placebo*
379. “doubl* blind*”
380. “singl* blind*”
381. assign*
382. volunteer*
383. “cohort stud*”
384. longitudinal*
385. follow-up
386. prospectiv*
387. retrospectiv*
388. “case control”
389. “case referent”
390. MeSH descriptor: [clinical trial] explode all trees
391. MeSH descriptor: [Cross-Over Studies] this term only
392. MeSH descriptor: [Placebos] this term only
393. MeSH descriptor: [Double-Blind Method] this term only
394. MeSH descriptor: [Single-Blind Method] this term only
395. MeSH descriptor: [Cohort Studies] explode all trees
396. MeSH descriptor: [case-control studies] this term only
397. 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396
398. 268 and 359 and 373 and 397

Web of Science

1. TOPIC = (diet$ or "mediterranean diet*" or dietetic or dietary or eat or eating or intake or nutrient$ or nutrition or vegetarian$ or vegan$ or macrobiotic$ or food$ or feed or feeding or cereal$ or grain$ or granary or wholegrain or wholewheat or "whole wheat" or wheat or wheatgerm or rye or barley or oat$ or root$ or tuber$ or vegetable$ or onion$ or spinach or chard or tomato* or pepper$ or carrot$ or beetroot or asparagus or garlic or pumpkin or sprouts or broccoli or cabbage$ or celery or ginger or potato* or crisps or fries or syrup or honey or fruit$ or apple$ or pear$ or banana$ or orange$ or grape$ or kiwi$ or citrus or grapefruit$ or pulses or bean$ or lentil$ or chickpea$ or legume$ or lupin$ or soy or soya or nut$ or almond$ or peanut$ or groundnut$ or seed$ or sesame or mustard or meat$ or beef or pork or lamb or poultry or chicken or turkey or duck or fish* or omega-3 or omega-6 or PUFA or fat$ or fatty or egg$ or bread or oil$ or omega or seafood or shellfish or crustacean$ or mollusc$ or dairy or milk or formula$ or hydrolysed or yoghurt or probiotic$ or prebiotic$ or butter or herb$ or spice$ or chilli* or condiment$ or beverage$ or "fluid intake" or water or drink* or pickled or bottled or canned or canning or smoked or preserved or preservative$ or nitrosamine or hydrogenation or fortified or nitrates or nitrites or ferment* or processed or antioxidant$ or "genetic modif*" or "genetically modif*" or cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserole* or broil or broiled or boiled or poach or poached or steamed or barbecue$ or chargrill* or salt or salting or salted or fiber or fibre or polysaccharide$ or starch or starchy or carbohydrate$ or lipid$ or "linoleic acid$" or sugar$ or sweetener$ or saccharin$ or aspartame or sucrose or xylitol or cholesterol or "hydrogenated lard" or "dietary protein$" or "protein intake" or "animal protein$" or "total protein$" or "vegetable protein$" or "plant protein$" or supplement$ or vitamin$ or retinol or carotenoid$ or tocopherol or folate$ or "folic acid" or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or polyphenol$ or phytoestrogen$ or genistein or saponin$ or coumarin$ or flavonoid$ or polyphenol$ or flavonol$ or flavone$ or isoflavone$ or catechin$ or "ascorbic acid$" or "hydroxy cholecalciferol$" or "hydroxycholecalciferol$" or tocotrienol$ or carotene$ or cryptoxanthin$ or lycopene$ or lutein$ or zeaxanthin$ or selenium$ or "organic diet$")
2. TOPIC = (allerg* or asthma* or wheeze or wheezing or "bronchial hyperresponsiveness" or "bronchial hyperreactivity" or "Forced expiratory volume" or "FEV1" or "FEV 1" or "FEV0.5" or "FEV 0.5" or "Forced vital capacity" or FVC or "Peak expiratory flow rate" or PEFR or eczema or neurodermatitis or rhinitis or "besniers prurigo" or rhinoconjunctivitis or hayfever or "hay fever" or poll$nosis or SAR or "pollen allergy" or conjunctivitis or "immunoglobulin e" or "Total IgE" or "autoimmune disease$" or diabetes or diabetic or "type 1" or "c$eliac disease" or "crohn* disease" or "Inflammatory Bowel Disease$" or "Ulcerative colitis" or (Lympho* NEAR/3 thyroiditi*) or (Thyroiditi* NEAR/3 autoimmune) or (Hashimoto* NEAR/3 (syndrome$ or thyroiditis* or disease$)) or (Thyroiditi* NEAR/3 (post-partum or postpartum)) or "Graves$ Disease" or "Basedow* disease" or "exophthalmic goiter$" or ("Still$ Disease" NEAR/3 (juvenile or onset)) or (Juvenile NEAR/3 arthriti*) or vitiligo or Psorias$s or (Arthriti$ NEAR/3 Psoria*) or "atopic disease" or "atopic dermatitis" or (food$ NEAR/3 sensiti*) or (food$ NEAR/3 toleran*) or (food$ NEAR/3 intoleran*) or ((aero or air*) NEAR/3 allergen$) or (aeroallergen$ NEAR/3 sensiti*) or (allergen$ NEAR/3 sensiti*) or "skin prick test*" or atopy or hypersensitive*)
3. TOPIC = (infant$ or (("one year$" or "two year$") NEAR/3 (old or age$)) or ((first or second or two) NEAR/3 "year$ of life") or (maternal NEAR/7 pregnan*) or (maternal NEAR/7 lactat*) or (mother$ NEAR/7 pregnan*))

4. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week$)
5. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month$)
6. 4 or 5
7. TOPIC = ((old or age$))
8. 7 and 6
9. 8 or 3
10. TOPIC = ("clinical trial$" or random* or factorial* or crossover* or placebo* or "doubl* blind*" or "singl* blind*" or assign* or volunteer* or "cohort stud*" or longitudinal* or follow-up or prospective* or retrospective* or "case control" or "case referent")
11. 1 and 2 and 9 and 10