REVIEW OF SCIENTIFIC PUBLISHED LITERATURE ON INFANT FEEDING AND DEVELOPMENT OF ATOPIC AND AUTOIMMUNE DISEASE

REVIEW B: TIMING OF INTRODUCTION OF ALLERGENIC FOODS TO THE INFANT DIET

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TABLE OF CONTENTS

1. Introduction

This 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 (FSA). Atopic conditions such as asthma, eczema, rhinoconjunctivitis and food allergy appear to have increased in prevalence in recent decades in many countries, and are now the leading causes of chronic illness in children and young adults living in the UK [1, 2 3 4 5]. The apparently rapid changes in disease prevalence, combined with data from migration studies, suggest that early-life environmental factors may be important modulators of atopic disease risk. Similar findings apply to the autoimmune diseases type I diabetes mellitus and Crohn's disease, which appear to have increased in prevalence in some countries [6]. Significant attention has focussed on early-life dietary exposures in relation to these atopic and autoimmune diseases due to the rapid changes in the human diet in recent decades, and the potential effects of such changes on intestinal and systemic immune development [7]. The gut associated lymphoid tissue is the largest collection of immune tissue in humans, and the most mature immune organ at the time of birth [8]. Hence enteral exposures in infancy are likely to be particularly important modulators of immune development and risk of immune-mediated disease. Although there is a large number of observational studies, some intervention trials and several systematic reviews in this area, they tend to focus on one specific aspect of diet and a limited number of immune outcomes. The purpose of this project was 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 outcomes and/or 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 B: Timing of introduction of allergenic foods to the infant diet

Increased attention has focussed on the role of timing of introduction of allergenic food intake and risk of atopic outcomes and autoimmune diseases in recent years. Initial studies of allergenic food avoidance were generally not thought to be successful in preventing food allergy or other allergic manifestations [9]. Later observational studies in humans suggested an association between early dietary introduction of allergenic foods and reduced risk of food allergy [10, 11]. Perhaps most compelling is the evidence from animal studies, which have shown for over 100 years that early introduction of allergens through the oral route can prevent future allergic sensitisation to such allergens [12]. This phenomenon of 'oral tolerance', first demonstrated in a guinea pig model of egg allergy, has not however been directly shown to occur in humans until recently. Significant intervention trials evaluating the potential to induce oral tolerance in humans in the context of coeliac disease and peanut allergy have received widespread attention, with discrepant findings [13] [14]. It is an important question whether oral tolerance can be induced in humans to other allergens, and whether any effects of oral tolerance induction in humans are antigen specific, and/or disease specific. For this review it is also important to assess whether the induction of oral tolerance is relevant to populations at high risk of disease, or whether study findings can be generalised and applied to the general UK population.

This review will address 2 key research questions, to help understand the potential role of timing of introduction of allergenic foods on an infant's risk of atopic outcomes or autoimmune disease. The review will use a similar methodological approach to that already employed for Reviews A and C.

1.2. Specific review questions addressed in Review B

B1. Does the timing of introduction of specific allergenic foods, into the infant diet during the first year of life, influence children's future risk of atopic disease, allergic sensitisation or autoimmune disease?

B2. Do such effects vary according to duration of exclusive/predominant or any breastfeeding?

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; commonly associated with 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.

Allergenic food introduction: introduction of one or more of the common allergenic foods to the diet of an infant up to and including 12 months age. Allergenic foods are defined as milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts and soybeans [15].

Early intervention trial: an intervention trial where the comparison made is between *early introduction of allergenic food* (intervention) versus either *no advice* or *advice to delay introduction of allergenic food* (control).

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

Longer term early intervention trial: an intervention trial where the intervention period is not restricted to the first week of life.

Nut: this collectively refers to the legume peanut (groundnut) and to tree nuts (eg hazelnut, almond, cashew).

Short term early intervention trial: an intervention trial where the intervention period is during the first week of life, and does not extend beyond that time period.

Standard intervention trial: an intervention trial where the comparison made is between *no advice* (intervention) versus *advice to delay introduction of allergenic foods* (control).

Trial sequential analysis: a method for assessing the statistical reliability of meta-analysis findings.

2. Executive Summary

The key findings of this review are summarised below, in relation to each of 7 outcome domains of interest – wheeze (including asthma and lung function), eczema, rhino-conjunctivitis, allergic sensitisation, food allergy, type 1 diabetes mellitus, and all other autoimmune diseases. We used the GRADE approach to assessing the strength of evidence, and specify in the text of the Executive Summary where judgements have been made that result in lower or higher grade evidence [16].

This is followed by a summary of the Methods used to identify studies, extract, analyse and appraise data, and a Discussion of the main findings in the context of existing literature. The 13 separate systematic reviews which provide the basis for this Executive Summary and constitute the substance of REVIEW B, can be accessed from Table 1 below.

Table 1 Individual study reports in relation to outcome domains of interest.

Outcome	Intervention trials	Observational studies
Wheeze	Wheeze Intervention.pdf	Wheeze Observational.pdf
Eczema	Eczema Intervention.pdf	Eczema Observational.pdf
Rhino-conjunctivitis	AR Intervention.pdf	AR Observational.pdf
Food Allergy	FA Intervention.pdf	FA Observational.pdf
Allergic Sensitisation	AS Intervention.pdf	AS Observational.pdf
Type 1 Diabetes Mellitus	INCLUDED IN AUTOIMMUNE DISEASE REPORT	TIDM Observational.pdf
Other Autoimmune Diseases	AID Intervention.pdf	AID Observational.pdf

2.1 Timing of introduction of allergenic foods, and Wheeze

Intervention trials: data from over 7,000 participants in 16 studies contributed to this report. Only 2 studies had a low overall risk of bias. The number of studies included in each analysis was small, especially for evaluation of egg, soya, nuts, fish and wheat introduction. Several analyses were dominated by multifaceted studies, where timing of allergenic food introduction was a small part of the intervention. One small study at high risk of bias found reduced wheezing at age 5-14 with soya milk formula and egg avoidance, compared to cow's milk formula during the first 9 months. This association was not supported by two other studies of cow's milk versus soya milk infant formula.

Observational studies: data from over 60,000 participants in 30 studies contributed to this report. Thirteen (43%) studies had a low overall risk of bias. The number of studies included in each analysis was small, and opportunities for meta-analysis were limited. We found evidence from 3 cohort studies with over 11,000 participants that fish introduction prior to 8-12 months is associated with reduced recurrent wheeze at age ≤4 years (OR 0.72 95%CI 0.59, 0.87; I2=0%). However 5 other studies with over 12,000 participants found no evidence for an association. There was no evidence for association with other allergenic foods, or with lung function..

Conclusion:

We found no evidence that timing of allergenic food introduction influences risk of wheezing, or lung function.

2.2 Timing of introduction of allergenic foods, and Eczema

Intervention trials: data from over 7,000 participants in 17 studies contributed to this report. Only 1 study had a low overall risk of bias. Data came mainly from studies of multifaceted intervention trials, or from studies comparing cow's milk with soya milk formula in infants. For most comparisons data were relatively sparse. We did not find any consistent evidence that timing of allergenic food introduction influences risk of eczema.

Observational studies: data from over 50,000 participants in 37 studies contributed to this report. Twelve (32%) studies had a low overall risk of bias. Few studies excluded participants with early onset eczema to account for reverse causation, and over 40% failed to adjust for potential confounders. Extreme or high statistical heterogeneity seen in many analyses may be related to mixed handling of confounders and infants with early onset eczema, but was sometimes unexplained despite similar approaches. Overall we found no evidence that timing of introduction of allergenic foods influences risk of eczema.

Conclusion:

We found no consistent evidence for associations between timing of introduction of allergenic foods and eczema.

2.3 Timing of introduction of allergenic foods, and Rhino-conjunctivitis

Intervention trials: data from over 6,000 participants in 13 studies contributed to this report. Only 2 studies had a low overall risk of bias. Data were sparse with high or extreme heterogeneity in several meta-analyses – mainly related to a single study which reported reduced Allergic Rhinitis (AR) with early soya introduction and egg avoidance, compared with early cow's milk introduction. Twelve other studies found no association between timing of milk or soya introduction and AR. Data for egg, fish, nut and wheat introduction were limited to studies of multiple dietary interventions, and showed no evidence of an effect on AR. We did not identify any intervention studies reporting Allergic Conjunctivitis.

Observational studies: data from over 20,000 participants in 12 studies contributed to this report. Four (33%) studies had a low overall risk of bias. Small numbers of studies contributed to individual analyses, and data were sparse for soya, egg and cereal and absent for nuts or 'any allergenic food'. We found LOW evidence from analysis of 4 studies with over 12,000 participants that early introduction of fish to the infant diet – before 6, 8, 9 or 12 months in the 4 studies - is associated with reduced Allergic Rhinoconjunctivitis (ARC) at age ≤ 4 (3 studies OR 0.59 95%CI 0.40, 0.87; I^2=59%) or age 5-14 (1 study OR 0.68 95%CI 0.47, 0.98). Sensitivity analysis of low risk of bias studies found the association between fish introduction and reduced rhinitis at age ≤4 years was not significant. We found no evidence for an association between timing of cow's milk, soya, egg or cereal introduction and ARC.

Conclusion:

There is LOW evidence from 4 observational studies, that fish introduction before 6-12 months may be associated with reduced risk of ARC at age ≤ 4 or 5-14. This association is not supported by intervention trials, although very little contributory information was available from such studies. There is no evidence of association for other allergenic food introduction.

2.4 Timing of introduction of allergenic foods, and Allergic Sensitisation

Intervention trials: data from over 6,000 participants in 17 studies contributed to this report. Four (24%) studies had a low overall risk of bias. Most analyses were dominated by studies of multiple interventions. We found no evidence that early introduction of allergenic foods influences Allergic Sensitisation (AS). For the egg introduction and egg sensitisation analysis, heterogeneity was due to an abstract publication which used specific IgE rather than skin prick testing. In sensitivity analyses of early egg introduction and allergic sensitisation to egg that excluded abstracts, or studies at high or unclear risk of bias, early egg introduction was associated with significantly reduced risk of allergic sensitization to egg.

Observational studies: data from over 20,000 participants in 20 studies contributed to this report. Eleven (55%) studies had a low overall risk of bias. Data from relatively few studies contributed to each analysis, but almost all data were from prospective cohort studies, and in several cases measures were taken to account for possible reverse causation in analyses. We found no consistent evidence that timing of introduction of cow's milk, soya, egg or wheat is associated with AS. We found VERY LOW evidence (-1 indirect outcome) from 3 studies with over 13,000 participants, that earlier introduction of fish – before 6-9 months - is associated with reduced AS to both any allergen and to food allergens.

Conclusion:

There is VERY LOW evidence for a relationship between fish introduction before 6-9 months and reduced AS, from observational studies. This association is not supported by intervention trials, although very little contributory information was available from such studies. There is no evidence of association for other allergenic food introduction.

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2.5 Timing of introduction of allergenic foods, and Food Allergy

Intervention trials: data from over 10,000 participants in 15 studies contributed to this report. Two (13%) studies had a low overall risk of bias. We found MODERATE evidence (-1 indirectness) that early egg introduction at 4-6 months reduces risk of egg allergy compared with later introduction (5 studies RR 0.56 95%CI 0.36, 0.87; I^2=36%), and MODERATE evidence (-1 indirectness; -1 imprecision; +1 strong effect size) that early peanut introduction at 4-11 months reduces peanut allergy (2 studies RR 0.29 95%CI 0.11, 0.74; I^2=66%). For egg introduction and egg allergy, heterogeneity was due to one abstract publication but findings were similar with exclusion of abstracts. For peanut introduction and peanut allergy, heterogeneity was attributed to differences between studies in treatment adherence. We found no evidence of similar associations for cow's milk or all allergenic food.

Observational studies: data from almost 40,000 participants in 18 studies contributed to this report. Seven (39%) studies had a low overall risk of bias. Data from relatively few studies contributed to each analysis. We found no evidence that timing of cow's milk introduction is associated with food allergy. We found LOW evidence (-1 imprecision, +1 dose-response relationship) that early egg introduction is associated with decreased egg allergy (1 study OR 0.29 95%CI 0.15, 0.56). We found no evidence that timing of introduction of other allergenic foods is associated with food allergy.

Conclusion:

Egg introduction at 4-6 months age and peanut introduction at 4-11 months age may reduce risk of Egg Allergy and Peanut Allergy respectively, compared with later introduction.

Grade of evidence: MODERATE.

We found no evidence for a relationship between timing of introduction of cow's milk, fish or wheat and risk of food allergy.

2.6 Timing of introduction of allergenic foods, and Type 1 Diabetes Mellitus

Intervention trials: data from over 3,500 participants in 2 studies contributed to this report. Both studies had unclear overall risk of bias. Data were limited to brief early cow's milk introduction in one study, and early gluten introduction in one study, both assessing the outcome clinical Type 1 Diabetes Mellitus (TIDM). We found no evidence for a relationship in either of these studies. We did not identify any intervention studies reporting the timing of other allergenic food introduction and risk of TIDM.

Observational studies: data from over 45,000 participants in 35 original studies contributed to this report. Twenty-six studies were case control studies. Just 12 (34%) studies had a low overall risk of bias. For some analyses retrospective studies found associations between early allergenic food introduction and increased TIDM risk, but for the same exposure/outcome, prospective studies did not confirm the association. For example cow's milk introduction before 3-4 months age was associated with increased TIDM in retrospective studies (14 studies OR 1.22 95%CI 1.04, 1.44; I^2=42%) but not in prospective studies (5 studies OR 0.92 95%CI 0.75, 1.13; I^2=0%). Overall we found no evidence that timing of cow's milk, egg, soya, fish or cereal introduction is associated with TIDM risk, although data were sparse for some of these exposures. No data were identified for timing of nut introduction and TIDM.

Conclusion:

We found no consistent evidence that timing of allergenic food introduction influences risk of TIDM.

2.7 Timing of introduction of allergenic foods, and Other Autoimmune Diseases

Intervention trials: data from almost 2,000 participants in 4 studies contributed to this report. One study had a low overall risk of bias. Data were limited to timing of gluten introduction at 4-6 months versus later and risk of coeliac disease, and the interaction between gluten introduction and breastfeeding status on coeliac disease. We found HIGH evidence of no association between timing of gluten introduction introduction and risk of coeliac disease (4 studies; RR 1.22 95% CI 0.81, 1.83; I^2=46%). We found no evidence for a relationship between breastfeeding status at the time of gluten introduction and coeliac disease in these studies. Two meta-analyses had moderate or high statistical heterogeneity, which was attributable to a single small study at high overall risk of bias, which reported significantly increased serological evidence of coeliac disease during early gluten introduction. Subsequent, larger studies at lower risk of bias showed that early gluten introduction may lead to earlier clinical manifestation of coeliac disease, but found no evidence that disease risk is increased. For the gluten introduction and coeliac disease analysis, heterogeneity was explained by one small study at high risk of bias, where the control group had not yet ingested gluten at the time of outcome assessment, so that coeliac disease or serology could not manifest. We did not identify any intervention studies reporting timing of other allergenic food introduction or other autoimmune outcomes.

Observational studies: data from 2 pre-existing systematic reviews including over 250,000 participants. We reviewed a further 14 original studies which included data not captured by the systematic reviews. Just two (14%) studies had a low overall risk of bias. We found no evidence that timing of introduction of cow's milk to the infant diet is associated with risk of Coeliac Disease (more or less than 3-4 months age) or Juvenile Idiopathic Arthritis (12 months), or that timing of gluten introduction (more or less than 6 months age) or

breastfeeding status at the time of gluten introduction are associated with Coeliac Disease or inflammatory bowel disease.

Conclusion:

We found no consistent evidence that introduction of cow's milk in the first 4 days of life, or before 3-4 months age, or introduction of gluten at 4-6 months, influences autoimmune disease risk, compared with later introduction.

Grade of evidence (for gluten introduction and coeliac disease): HIGH

We found no evidence that breastfeeding status at the time of gluten introduction influences autoimmune disease risk, and no evidence that introduction of cow's milk before 12 months influences risk of juvenile idiopathic arthritis.

3. Methods

3.1. Inclusion Criteria

3.1.1. Types of study included

We included recent high quality systematic reviews published from 2011 until the search date (25th July 2013; updated on 8th March 2016). 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 [17] and extracted data from systematic reviews with revised AMSTAR score ≥32. For Review B we identified three eligible recent systematic reviews.

We included other research studies published at any time prior to the search date (25th July 2013; updated on 8th March 2016). 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 available from a recent high quality systematic review we did not extract the same data from original studies. Where a large number of intervention trials/ participants (eg over 20 trials and over 5000 participants) were identified, and clear conclusions could be made from intervention trial data, 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.

3.1.2. 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 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 either the general UK population or the UK population at high familial risk of relevant outcomes. We did not exclude studies on the basis of including specific ethnic groups, or of studying high risk infants. Over half UK-born infants can be considered at high risk for allergic disease due to family history; and studies of autoimmune disease prevention are hard to undertake in the general population due to their low prevalence.

3.1.3. Interventions/ exposures

3.1.3.1. Review question B1

Does the timing of introduction of specific allergenic foods (cow's milk, hen's egg, peanut, tree nuts, fish/seafood, wheat, soya), into the infant diet during the first year of life, influence children's future risk of atopic disease, allergic sensitisation or autoimmune disease?

Definition of allergenic foods: In this review, allergenic foods are defined as milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts and soybeans [15]. For intervention trials we included multifaceted interventions where timing of allergenic food introduction was only part of the intervention, but planned to undertake subgroup analysis excluding such studies where appropriate. We included studies of timing of introduction of 'gluten', or 'cereal' if the

definition of cereal included wheat, rye, barley and/or oats, but did not include studies of timing of introduction of 'cereal' defined as non-gluten containing cereals such as rice. In the reports we refer to gluten/wheat/cereal introduction as 'cereal' in the observational study reports, and as 'wheat' in the intervention study reports since intervention trials more frequently used wheat or wheat avoidance as the intervention, whereas observational studies more frequently assessed intake of any gluten-containing cereal as the exposure of interest.

Definition of timing of allergenic food exposure interventions: In intervention trials for this review we included studies comparing single brief early allergenic food exposure (defined as interventions limited to the first week of life), but analysed these separately from more sustained allergenic food exposures. We included sustained early exposure to single or multiple allergenic foods, where multiple allergenic food interventions were included in analyses pertaining to all allergenic foods used. We included studies of multiple simultaneous dietary and/or non-dietary interventions, where allergenic food avoidance/introduction was just a component of the intervention package. Non-dietary interventions included tobacco smoke and house dust mite avoidance measures. This means that for many analyses there is uncertainty about the directness of any associations found between intervention group and atopic/autoimmune outcomes.

Current UK Government advice is for the introduction of allergenic food into the infant diet to be delayed until 6 months of age or later. In this report we describe intervention studies of two types:

'Standard' intervention trials where comparisons have been made between giving no advice about introduction of allergenic foods (intervention), with advice to deliberately delay introduction of allergenic foods (control).

'Early' intervention trials in which comparisons have been made between deliberate early introduction of allergenic food(s) (intervention), with either no advice about introduction, or advice to delay introduction of allergenic foods (control).

For our purposes in both types of study the early or unrestricted introduction of allergenic foods is considered as being the 'intervention', and the delayed or standard introduction of allergenic foods as being the 'control'. The reason for this is so that, where appropriate, both types of study can be incorporated into the same meta-analysis.

This means that for for some studies there is uncertainty about the degree to which timing of allergenic food introduction differed between intervention and control groups. For example in some settings 'standard' introduction of allergenic foods may be delayed, and in others 'standard' introduction may be early [10].

3.1.3.2. Review question B2

Do any associations between timing of introduction of allergenic food and risk of atopic/autoimmune disease vary according to duration of exclusive/predominant or any breastfeeding?

Breastfeeding definition: Where possible, we planned to characterise studies according to whether they defined exclusive/predominant breastfeeding according to the WHO definition.

3.2. 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 8th March 2016. 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 B are listed at the end of this document, 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 8th March 2016 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 (Lee et al., 2012). 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 arthritis 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.

3.3. Study Outcomes

We selected atopic outcomes and autoimmune disease 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 [18]. 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 first 1 year. For each outcome measure in this review, there is more than one possible method of assessment. We therefore included our preferred method of

assessment for each outcome, which is the *a priori* 'primary outcome measure', assessed at the optimal age as defined above.

3.3.1. 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. For the analysis of food allergy in relation to timing of allergenic food introduction (Review B) we also included reports of allergy to fish, wheat, soya and tree nuts in relation to timing of introduction of the same food. We did not include reports of 'food intolerance' that we judged were unlikely to meet current definitions of food allergy [19].

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 [20]. We combined data for skin prick and specific IgE testing 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).

3.3.2. 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 [21], 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 [22].
6. *Vitiligo* - defined as a medical diagnosis.

Primary assessment: medical diagnosis using the Vitiligo European Task Force 2007 criteria or similar [23].

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

3.4. Study selection and data extraction

3.4.1. Study selection

Title and abstract screening was undertaken in duplicate by a team of 8 researchers (RB, VGL, DI, NG, KJ, JC, ZR, SC). 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 March 2016. 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.

3.4.2. 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.

3.4.3. 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. Data cleaning was undertaken by DI, SC and RJB. Data on timing of allergenic food introduction were extracted independent of exposure cut-offs used in the studies. However, in order to have homogeneous exposure

reference group(s), data were only included in meta-analysis where the reference group (cut-off) of allergenic food introduction was complete ie 'less than' a certain duration. Studies evaluating timing of 'any solid food' introduction, or foods other than our predefined list of allergenic foods into the infant diet, and studies assessing different levels of allergenic food intake during infancy, are included in separate reports – REVIEWS A and REVIEW C (PART II and Observational reports).

Where more than one exposure group was compared with the reference group (≤ than a specific cut-off) in relation to the same outcome at the same age, we chose the exposure furthest from the cut-off point. For example a study reporting the relationship between timing of introduction of allergenic food and wheeze at age 2 years, with data for ≤4 versus 5-7 and ≤4 versus >7 months duration, we would include the comparison ≤4 versus >7 months. This would be grouped for meta-analysis with studies comparing ≤4 versus >4 months duration. We used the following exposure cut-offs for timing of introduction of allergenic foods, which were selected based on the distribution of the data presented in published reports so as to maximise our ability to undertake meta-analysis: ≤ 0-2 vs. >0-2; ≤3-4 vs >3-4; ≤5-7 vs.>5-7 ; ≤8-12 vs. >8-12 and ≤ 12-24 vs. >12-24 months duration. Data that could not fit in any group were not included in meta-analysis, but were reported narratively. The outcomes of both meta-analysed and narratively reported studies were considered together when interpreting data and making conclusions.

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 binary measure for the same outcome, we took a hierarchical approach to selection of data for analysis:

Hazard ratio (time to event) data were selected where available.

Cumulative incidence or lifetime prevalence ie 'disease ever' were selected if no hazard ratio was available.

Point prevalence data (eg 'disease in the last 12 months') were selected if no cumulative or lifetime prevalence measure was available.

For non-clinical outcomes allergic sensitisation and lung function, we selected point prevalence in preference to cumulative measures.

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 (eg 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, and if equal numbers were assessed we chose the timepoint with the greatest number of outcome events reported. 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 or for allergic sensitisation due to sparse data which didn't allow for meaningful comparisons when divided by age group. 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 in the relevant section of each report.

3.5. Risk of bias (quality) assessment

3.5.1. Review level bias

Publication bias was assessed using funnel plots and Egger's test, for those meta-analyses with ≥10 studies included. 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.

3.5.2. 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) [24]. 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. The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence methodological checklist for cohort and case-control studies respectively [25]. Key domains were Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for characteristic differences between participants and non-participants), Assessment Bias (low if validated and reliable tools were used to assess exposure and/or outcome), and

Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis). Observational studies 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 confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, maternal education/ socioeconomic status, smoking and disease risk. For all studies we also assessed possible Conflict of Interest, judged 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. For all study reports, we created a summary Table of Study Characteristics with key study features, and a separate summary Risk of Bias Figure showing the risk of bias for all included studies – whether included in meta-analyses or reported in the narrative table.

3.6. 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 summary. 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, and analyses of observational studies were stratified as prospective (cohort or nested case control) or retrospective (other case control or cross-sectional) study design.

3.6.1. Data extraction

Data were extracted either using raw frequencies, crude estimates of effect (including odds ratios, risk ratios, incidence rate ratios, hazard ratios, mean differences) or as adjusted estimates of effect. Adjusted estimates of effect were used in preference for primary analyses, where available. Random effect meta-analyses were performed to allow for heterogeneity between studies.

3.6.2. 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.

3.7. Data analysis

For rare outcomes (ie autoimmune outcomes) observational studies reporting Odds Ratios (OR) and Risk Ratios (RR) were combined in meta-analysis; for common outcomes (ie atopic

outcomes) OR, RR and HR data were reported separately. Pooled results for binary outcomes from intervention studies are presented as Risk ratios calculated from the frequencies given in the study; for observational studies as odds ratios – both with 95% confidence intervals as the vast majority of cohorts, case controls and cross sectional studies reported this measure of effect. 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) for pooled RR in the statistical programme R version 3.1.0 (2014-04-10 https://www.r-project.org/ Free Software Foundation, Boston, MA). Pooled results for continuous outcomes measured using similar scales are presented as mean differences with 95% confidence intervals. Where different scales were pooled across studies, we planned to report results using standardised mean differences. Where the only information given in the study was mean (SD) exposure in diseased and non-diseased children, those were used for calculating pooled mean differences between groups. Key findings from intervention trials are presented in Summary of Findings tables similar to those used by the Cochrane Collaboration [26].

3.7.1. 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. For observational study reports, we planned and undertook stratified analysis according to type of data - unadjusted versus adjusted data. Adjusted data were used preferentially in primary analyses. Stratified analysis was undertaken of all unadjusted data available and all adjusted data available separately to help understand the potential influence of confounding on analysis results. We also 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 stratified all meta-analyses as prospective versus retrospective study design.

For some reports, further specific subgroup analyses were undertaken appropriate to the outcome of interest – for example in type 1 diabetes (TIDM) meta-analyses we planned a subgroup analysis of serological versus clinical TIDM as an outcome measure, and in the Allergic Sensitisation meta-analyses we planned a subgroup of specific IgE versus Skin Prick Test as outcome measure.

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3.7.2. 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 human diet and the prevalence of different outcomes 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 by year of assessment.

3.7.3. Trial sequential analysis

Post hoc trial sequential analysis (TSA) was used to quantify statistical reliability of moderate or high certainty review findings using 2-sided 5% significance, 80% power and control event rates from included studies to estimate optimal heterogeneity-adjusted and non-adjusted information sizes needed to identify relative risk reductions of 10, 20 and 30%. TSA

quantifies statistical reliability of data in a cumulative meta-analysis in a similar way to an interim analysis in a single randomized clinical trial.

3.8. 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 FSA, 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.

3.9. Differences between the protocol and the 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 – NT-M, SC, UN, NG, ZR, JC, KJ, EA.

4. Results

4.1. Overview of recent high quality systematic reviews

Our search results are summarised in the PRISMA flow chart Figure 1.

Figure 1 - PRISMA for Existing Systematic Re

We identified 469 titles after removing duplicates, of which 26 were considered to be a report from a relevant or potentially relevant systematic review after title and abstract screening. All these studies underwent full text review and revised AMSTAR scoring by 2 authors independently (VGL, RJB). Two studies were only available in Chinese, and these were scored by a native Chinese speaker Dr Sze-Chin Tan, Consultant Allergist from Tan Tock Seng Hospital Singapore, who was trained in the revised AMSTAR scoring procedure prior to undertaking this task. Of the 26 scored studies, 8 were eligible for inclusion in the project overall, of which 1 was relevant to Review B. Eleven studies were excluded due to low AMSTAR score. One study was not a systematic review. Six studies were excluded because they were either protocols for a systematic review (n=2) or were abstract publications with insufficient detail to establish the AMSTAR score or sufficient detail regarding study outcomes (n=4). The updated search on 8th March 2016 identified 5 new systematic reviews, one of which was relevant to Review B and had R-AMSTAR score ≥32. A summary of R-AMSTAR scores for existing systematic reviews is shown in Table 2, and a summary of the 2 included reviews is shown in Table 3. Data from the 2 prior systematic reviews are included in the relevant section of this report (Autoimmune Disease Observational report).

4.2. Systematic review of original studies

Our search results are summarised in the PRISMA flow chart Figure 2.

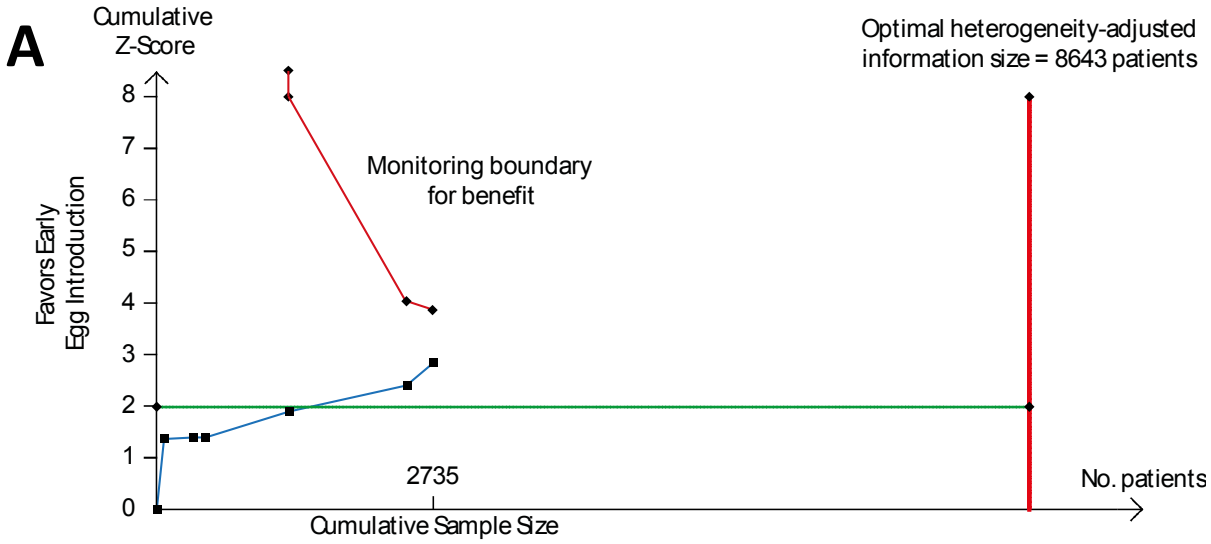
Figure 2. PRISMA Review B Original Title

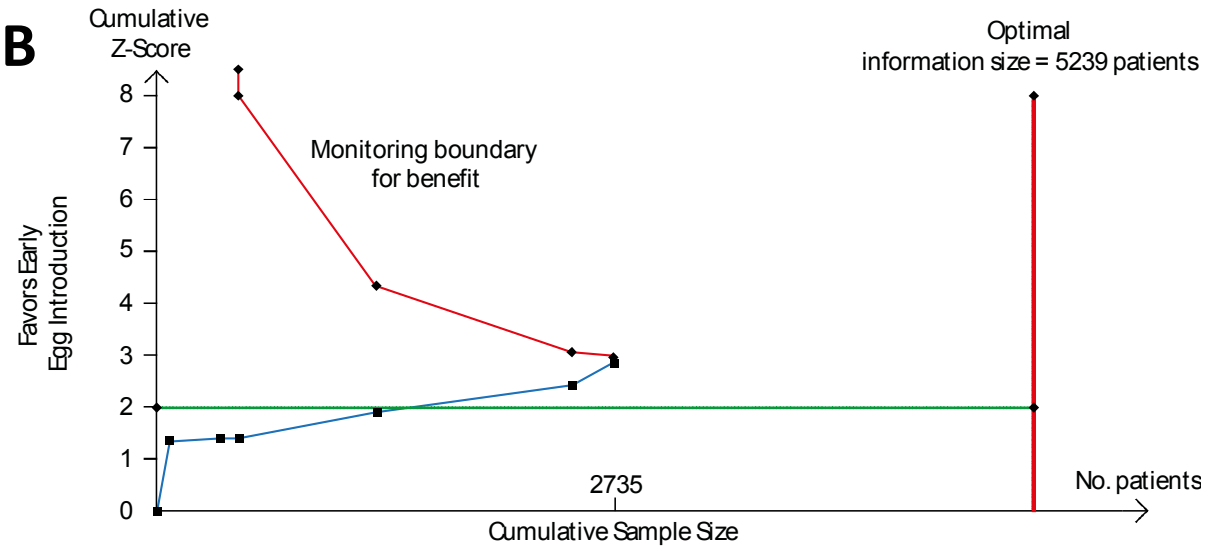
We identified 46 relevant intervention trials (25 original studies), 96 cohort studies (69 original studies), 6 nested case control studies (5 original studies) and 56 case control or cross-sectional studies (50 original studies) for inclusion in Review B. Numbers refer to the number of eligible titles, rather than number of original studies. These numbers include 12 intervention trial and 19 observational study titles identified from the updated search on 8th March 2016. Detailed findings, analyses and discussion for the 13 separate systematic reviews are shown in the attached reports (Table 1), and summarised in the Executive Summary. Key findings are summarised in the Summary of Findings Table (Table 4).

4.3. *Post hoc* analyses

Trial Sequential Analysis was undertaken for findings with HIGH or MODERATE certainty. Peanut introduction and peanut allergy were not evaluated using TSA, due to insufficient data in the meta-analysis to estimate a sufficient number of points for the monitoring boundaries. There were also insufficient data to perform TSA for 10% or 20% relative risk reduction for other findings. Whether early egg introduction was associated with a 30% reduction in risk of egg allergy using TSA was assessed. The heterogeneity-adjusted and non-adjusted optimal information sizes for detection of a 30% relative risk reduction for egg allergy were 8,643 and 5,239 study participants respectively. TSA for this outcome is shown in Figures 3A and 3B respectively.

Figure 3. *Post hoc* Trial Sequential Analysis of early egg introduction and risk of egg allergy

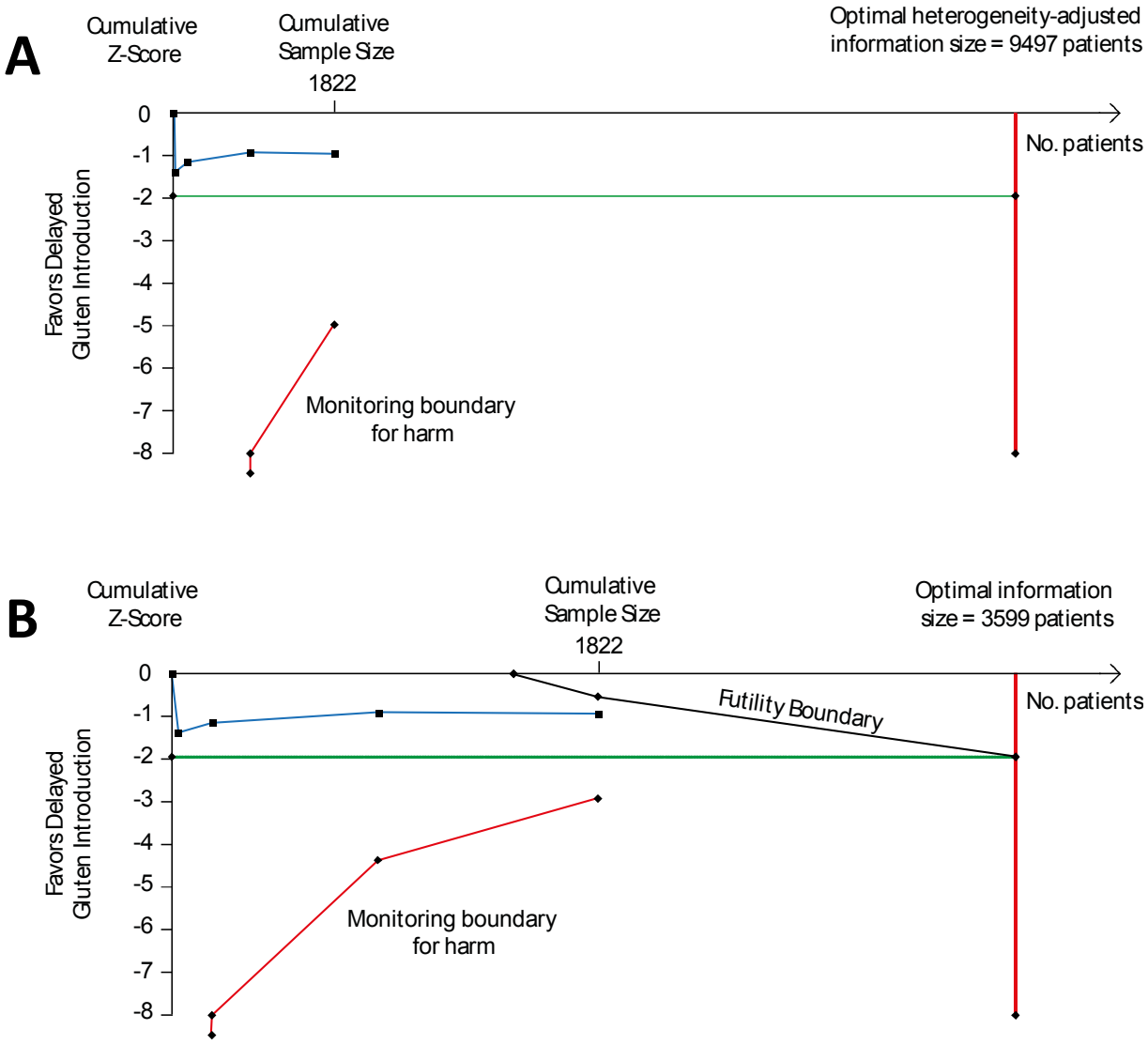




Although the conventional line of statistical significance was crossed (z=1.96) in both analyses, the optimal information size was not reached in either case. The cumulative z-score did not cross the monitoring boundary, although it was close in non-adjusted TSA. It cannot be confidently concluded that early egg introduction reduces egg allergy by at least 30%, and further trials are required to more precisely quantify the treatment effect.

TSA was also used to evaluate whether early gluten introduction increases coeliac disease risk by 30%. The heterogeneity-adjusted and non-adjusted optimal information sizes for detection of a 30% increase in relative risk for coeliac disease were 3,599 and 9,497 study participants respectively. TSA for this outcome is shown in Figures 4A and 4B respectively.

Figure 4. *Post hoc* Trial Sequential Analysis of early gluten introduction and risk of coeliac disease

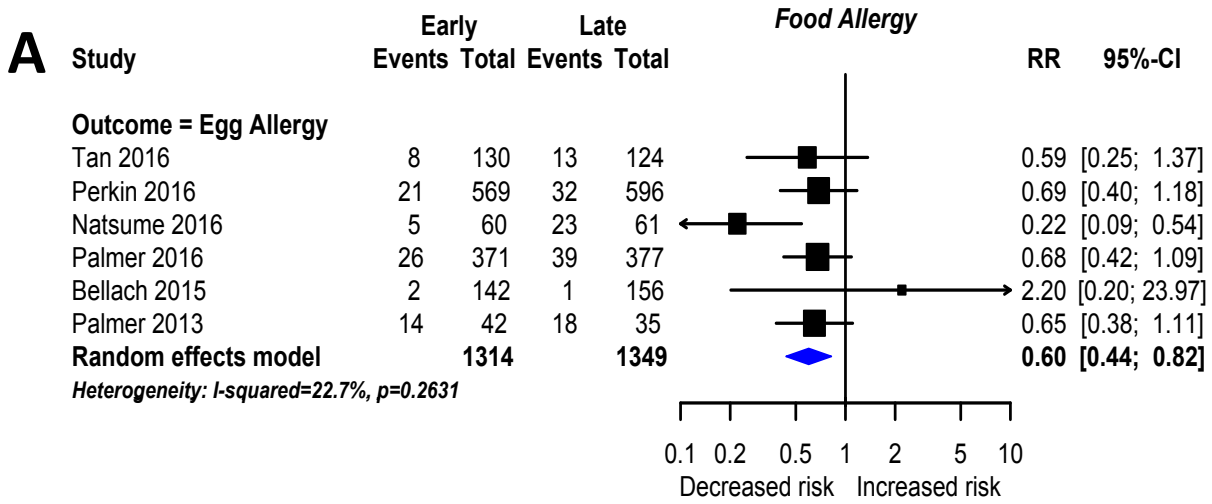


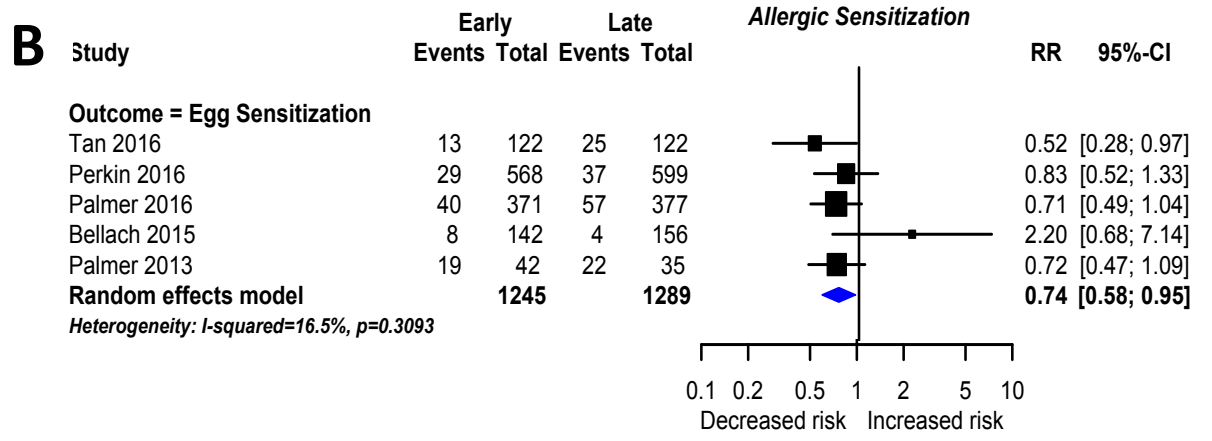
The conventional line of statistical significance was not crossed and the optimal information size was not reached. The cumulative z-score was close to the futility boundary in non-adjusted TSA. It cannot be confidently concluded that further studies of timing of gluten introduction and risk of coeliac disease are futile.

Finally primary analyses for egg introduction and risk of egg allergy were repeated on 29th August 2016, incorporating data from the study of Palmer et al 2016[57] published on 20th

August 2016 Data from Palmer et al 2016 were also included in the TSA analyses cited above. Meta-analysis findings for egg allergy and egg sensitization including the data of Palmer 2016 are shown in Figures 5A and 5B respectively. Findings for egg allergy are similar to those of the meta-analysis without Palmer 2016 , but for allergic sensitization the pooled effect becomes statistically significant after including Palmer 2016 data (Figure 5B).

Figure 5. Early egg introduction and risk of egg allergy or egg sensitisation





5. Discussion

In these systematic reviews of timing of allergenic food introduction we found no evidence for an association with autoimmune diseases, and mixed evidence of a relationship between the exposures and atopic outcomes. For most analyses we were unable to completely exclude clinically important effects due to wide confidence intervals, and for intervention study reports, the studies contributing to meta-analyses often had quite heterogeneous interventions. These ranged from early short term (3-4 days) introduction of an allergenic food, through early sustained introduction of single or multiple allergenic foods to 'standard' introduction where the control group were advised strict allergenic food avoidance until a certain age, and multifaceted studies which also included other dietary components +/- environmental control measures such as tobacco smoke and house dust mite avoidance. Thus for some analyses the conclusions must be guarded due to the indirect nature of the intervention. Indirectness was also an issue in the populations studied, since several intervention trials studied specific populations with either active allergic disease, absence of allergic sensitisation to the intervention food, or both. Key findings in this report were:

- HIGH grade evidence that early gluten introduction at 4-6 months does not influence risk of coeliac disease, compared with later introduction.

- MODERATE grade evidence that early introduction of egg at 4-6 months is associated with reduced egg allergy, and that early introduction of peanut at 4-11 months is associated with reduced peanut allergy, compared with later introduction of these foods.

- LOW grade evidence that early fish introduction before 6-12 months is associated with reduced ARC at age ≤4 and 5-14 years

- VERY LOW grade evidence that early fish introduction before 6-9 months is associated with reduced AS

The relationship seen between fish introduction and ARC or AS needs to be interpreted in the context of the findings of review C, where we identified MODERATE evidence from intervention trials that fish oil supplementation during pregnancy/lactation reduces risk of allergic sensitisation to egg during infancy. Together these data suggest that the known anti-inflammatory effects of omega-3 polyunsaturated fatty acids may be able to prevent allergic sensitisation and associated inflammatory disease when exposure occurs early in life.

The strongest evidence seen in this report is for associations between early allergenic food introduction and food allergy to the same food. These were seen for egg (MODERATE evidence) and peanut (MODERATE evidence) but not for other allergenic foods, nor indeed for 'multiple allergenic foods'. The evidence base for a relationship between early allergenic food introduction and food allergy to the same food is limited to a relatively small number of studies, and is not consistent between different food allergens. It is however consistent with a large body of data from experiments in different animal models, where the principle of 'oral tolerance' is well established – that early enteral exposure to allergens is effective for preventing sensitisation to the same allergen [12 28]. The evidence we identified in this report suggests that any such effects in humans are antigen-specific, with no data showing early introduction of one allergenic food influences the development of allergy to a different allergenic food. Trial sequential analysis emphasised that the data for peanut introduction and peanut allergy are limited (TSA was not possible due to a paucity of data), and supported the egg/egg allergy and gluten/coeliac disease findings. Here non-adjusted TSA showed that data for egg/egg allergy do not quite reach the optimal information size, and data for gluten/coeliac disease do not quite reach the futility boundary – suggesting that further trials

in this area are still worthwhile, in order to have increased certainty in the effect estimates for these findings.

We found no evidence that timing of allergenic food introduction influences risk of autoimmune disease. Evidence was limited to a small number of allergenic foods and diseases. The strongest evidence was found in relation to coeliac disease, where HIGH grade evidence from intervention trials suggested that early gluten exposure leads to earlier clinical manifestation of coeliac disease, but does not overall lead to increased coeliac disease. Our findings are consistent with the two systematic reviews of allergenic food introduction and coeliac disease which we identified and appraised within the autoimmune disease observational studies report [29, 2].

6. Conclusions

These data provide HIGH evidence that early gluten introduction from 4-6 months does not influence risk of coeliac disease, and MODERATE evidence that early egg and peanut introduction to the infant diet – from 4-6 months for egg, and 4-11 months for peanut - may reduce egg and peanut allergy respectively. There is LOW evidence that fish introduction before 6-12 months may reduce allergic rhinoconjunctivitis, and VERY LOW evidence that fish introduction before 6-9 months may reduce allergic sensitisation.

7. Acknowledgements

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Table 2 Quality assessment of recent systematic reviews using R-AMSTAR scoring.

Author/Reference	VGL Score	BB Score	CONSENSUS
Antico [30]	19	14	Exclude
Braeger [31]	30	29	Exclude
Brew [32]	**35**	**37**	Include – Review A
Cardwell [33]	31	25	Exclude
Christesen [34]	24	25	Exclude
De Silva [5]	26	29	Exclude
Dick [35]	22	19	Exclude
Doege [36]	28	21	Exclude
Flohr [37]	19	19	Exclude
Foolad [38]	18	22	Exclude
Gunaratne [39, 40]	Protocol and Abstract publication only		
Henricksson [41]	18	24	Exclude
Kheirkhah [42]	Abstract publication only		
Klemens [43]	**36**	**35**	Exclude – Review C
Kramer [44]	**38**	**40**	Include – Review A
Kramer [45]	**37**	**40**	Exclude – Review C
Kremmyda [46]	21	20	Exclude
Middleton [47]	Abstract publication only		
Osborne [48]	Abstract publication only		
Osborne [49]	**38**	**40**	Exclude – Review C
Pelucci [50]	**33**	**36**	Exclude – Review C
Patelarou [51]	23	24	Exclude
Pinto-Sanchez [58]	40	32	Include – Review B
Schindler [52]	Protocol only		
Schmitt [53]	Not a systematic review		
Szajeweska [29]	**36**	**35**	Include – Reviews A and B
Silano (3)	**30**	**25**	Exclude
Tang [54]	**34***		Exclude – Review C
Waidyatillake [55]	24	25	Exclude
Wang [56]	31*		Exclude

A score of ≥32 was required for inclusion; * Chinese language, scored by Dr Sze-Chin Tan

Table 3 Characteristics of included systematic reviews

Study Relevant SR	**Databases searched**	**No. studies No. (range) participants**	**Study designs included**	**Population**	**Intervention/ Exposure(s) Comparator(s)**	**Outcomes relevant to the project**	**Subgroup analyses relevant to project**
Szajewesk a [29] Review A Review B	CENTRAL, MEDLINE, EMBASE (up to July 2012)	12 studies 266,728 participants *7 studies relevant to review B*	3 cohort studies 5 case control studies	Infants at population risk or increased risk of developing Coeliac disease (defined by HLA status, first-degree relative with coeliac disease or type 1 diabetes mellitus)	• Time of gluten introduction • Breastfeeding during gluten introduction	• Coeliac disease • Coeliac autoantibodies (anti-TG2 or EMA)	Nil
Pinto-Sanchez [58] Review B	CENTRAL, MEDLINE, CINAHL, DARE, EMBASE, SIGLE (up to January 2014)	15 studies 429,069 participants All studies relevant to review B	2 intervention trials 10 cohort studies 1 case-control study	Infants at high or normal risk of Coeliac disease	• Time of gluten introduction • Breastfeeding during gluten introduction	• Coeliac disease • Coeliac autoantibodies (anti-tTG or EMA)	Nil

Table 4 Summary of Findings

GRADE of evidence assessment								Summary of findings		Absolute Risk Reduction	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Estimate**	**GRADE of evidence**	**Control Risk (Cases per 1000 population)**	**Risk Difference (Cases per 1000 population)**
Outcome: Allergic Rhinitis **Intervention vs. comparator: Early introduction of fish versus later introduction of fish**											
4 observational studies	4 PC	Not serious 1 study at high risk of bias; all studies with low risk of conflict of interest	Not Serious I^2=59% (P=0.086), study estimates varying from 0.45 to 0.77 but all 4 studies statistically significant, and heterogeneity was reduced when early onset eczema cases were excluded from analysis due to potential reverse causation	Not serious Studies all undertaken in Scandinavia. 3 studies were in representative birth cohorts, 1 in a birth cohort selected for high risk of TIDM	Not serious 95% CI are wide, but not close to 1, and together the 4 studies include over 12,000 participants	Insufficient studies to undertake formal testing of publication bias.		**AR ≤4years** **OR = 0.59** **(0.40 to 0.87)** **AR 5-14 years** **HR = 0.68** **(0.47 to 0.98)**	⊗⊗○○ **Low**	**AR ≤4years** **50 (normal risk)** **100 (high risk)** **AR 5-14years** **100 (normal risk)** **200 (high risk)**	**18 cases less (6 to 30)** **38 cases less (12 to 57)** **32 cases less (2 to 53)** **64 cases less (4 to 106)**
Outcome: Allergic Sensitization to any allergen, any food **Intervention vs. comparator: Early introduction of fish versus later introduction of fish**											
5 observational studies	5 PC	Not serious 2 studies ~700 participants high risk of bias; 3 studies (~ 13,000) low risk of bias; no conflict of interest	Not serious Extreme heterogeneity for meta-analysis of inhalant sensitization; consistent findings for other sensitizations	Serious Allergic sensitization is an indirect measure of disease	Not serious 3 studies at low risk of bias were consistent - OR/HR from 0.41 to 0.78, and included over 13,000 participants	Insufficient studies to undertake formal testing of publication bias.		**AS any allergen** **OR = 0.75** **(0.64 to 0.88)** **AS any food** **OR = 0.52** **(0.37 to 0.73)**	⊗○○○ **Very Low**	**AS any allergen** **200 (normal risk)** **400 (high risk)** **AS any food** **100 (normal risk)** **200 (high risk)**	**42 cases less (20 to 62)** **67 cases less (30 to 101)** **45 cases less (25 to 61)** **85 cases less (46 to 115)**
Outcome: Egg allergy **Intervention vs. comparator: Early introduction of egg versus later introduction of egg**											
6 intervention studies (5 of which provided data for meta-	6 RCT	Not Serious 1 study at high risk of bias, no	Not serious I^2=36% (P=0.18). Study estimates vary from 0.22 to 0.69 for the studies at	Serious 3 studies only recruited infants without egg	Not serious 95% CI for RR is wide. Trial sequential	Insufficient studies to undertake formal testing of publication		**RR = 0.56** **(0.36 to 0.87)**	⊗⊗⊗○ **Moderate**	**54 (normal risk)** **100**	**24 cases less (7 to 35)** **44 cases**

analysis)		studies at high risk of conflict of interest	low risk of bias	sensitization; 1 study only infants with eczema; 1 study used multiple allergenic foods	analysis suggests that optimum information size has not yet been reached	bias				**(high risk)** **500 (very high risk)**	**(13 to 64)** **220 cases (65 to 320)**
Outcome: Nut allergy **Intervention vs. comparator: Early introduction of nut versus later introduction of nut**											
2 intervention studies	2 RCTs	No Neither study had a high risk of bias or conflict of interest	Not Serious I^2=66% (P=0.09), study estimates vary from 0.49 to 0.19 but heterogeneity is likely to be explained by differences in participant adherence to the intervention	Serious 1 study only recruited infants with egg allergy or eczema, and without high-level peanut sensitization; 1 study used multiple allergenic foods	Serious 95% CI for RR is wide	Insufficient studies to undertake formal testing of publication bias	GRADE of evidence increased due to the strong effect size	**RR = 0.29 (0.11 to 0.74)**	⊗⊗⊗○ **Moderate**	**25 (normal risk)** **170(high risk)**	**18 cases less (6 to 22)** **121 cases less (44 to 151)**
Outcome: Type I Diabetes Mellitus **Intervention vs. comparator: Early introduction of cow's milk versus later introduction of cow's milk**											
33 observational studies	7 PC 1 NCC 25 CC	Not Serious 12 studies with high overall risk of bias; all studies with low risk of conflict of interest	Serious High or extreme statistical heterogeneity in several analyses. In some meta-analyses significant associations were seen for retrospective, but not for prospective studies	Not Serious All but one prospective reported islet autoimmunity as a surrogate for TIDM. Retrospective studies used clinical diagnosis	Not Serious Studies included over 40,000 participants. 95% CI for meta-analyses of prospective studies were wide	No Funnel plots and Egger's test do not indicate evidence of publication bias		**Prospective Studies** **CM ≤ 0-2m** **OR = 1.20 (0.53 to 2.71)** **CM ≤ 3-4m** **OR = 0.92 (0.75 to 1.13)** **CM ≤ 5-7m** **OR = 1.88 (1.05 to 3.39)**	⊗○○○ **Very Low**	**CM ≤0-2m** **1 (normal risk)** **10 (high risk)** **CM ≤3-4m** **1 (normal risk)** **10 (high risk)** **CM ≤5-7m** **1 (normal risk)** **10 (high risk)**	**0.2 cases more (0.5 less to 1.7 more)** **2 cases more (4.7 less to 16.6 more)** **0.1 cases less (0.2 less to 0.1 more)** **0.8 cases less (2.5 less to 1.3 more)** **0.9 cases more (0.0 to 2.4)** **8.6 cases more (0.5 to 23.1)**
Outcome: Coeliac disease **Intervention vs. comparator: Early introduction of gluten versus later introduction of gluten**											

4 intervention studies	4 RCT	Not serious 1 study with high risk of bias; all studies with low or unclear risk of conflict of interest	Not Serious I^2=46% (P=0.13), due to 1 small study with high risk of bias; other estimates from 0.96 to 1.66	Not Serious Two studies used only serology, but this surrogate is highly correlated with clinical disease	Not Serious significant benefit unlikely – lower bound RR 0.81, or 0.85 with high risk of bias study excluded	Insufficient studies to undertake formal testing of publication bias.	All studies included high risk patients based on family history and/or genotype	**RR = 1.22 (0.81 to 1.83)**	⊗⊗⊗⊗ **High**	**10 (normal risk)** **100 (high risk)**	**2.2 cases more (1.9 less to 8.3 more)** **22 cases more (19 less to 83 more)**

Appendix 1 Search Strategies for other systematic reviews

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

1.1. 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. Coeliac 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"

1.2. 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. coeliac 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"

1.3. 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 [Coeliac 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

Appendix 2 Search Strategies for original articles (Review B)

2.1. Medline

1. complementary food?.ab,ti.
2. (introduc$ adj2 food?).ab,ti.
3. wean$.ab,ti.
4. Weaning/
5. solid?.ab,ti.
6. semi-solid?.ab,ti.
7. baby food?.ab,ti.
8. Infant Food/
9. Infant Nutritional Physiological Phenomena/
10. breast feeding.ab,ti.
11. breastfeeding.ab,ti.
12. breast fed.ab,ti.
13. breastfed.ab,ti.
14. Breast Feeding/
15. Milk, Human/
16. formula?.ab,ti.
17. hydrolysed.ab,ti.
18. bottlefed.ab,ti.
19. bottle fed.ab,ti.
20. (bottle adj3 feed$).ab,ti.
21. Infant Formula/
22. Bottle Feeding/
23. liquid?.ab,ti.
24. milk.ab,ti.
25. Milk/
26. egg?.ab,ti.
27. Egg Proteins/
28. Egg Proteins, Dietary/
29. nut?.ab,ti.
30. peanut?.ab,ti.
31. almond?.ab,ti.
32. (brazil? adj5 nut?).ab,ti.
33. walnut?.ab,ti.
34. pecan?.ab,ti.
35. pistachio?.ab,ti.
36. cashew?.ab,ti.
37. hazelnut?.ab,ti.
38. macadamia?.ab,ti.
39. Nuts/
40. Arachis hypogaea/
41. Prunus/
42. Bertholletia/
43. Juglans/

44. Carya/
45. Pistacia/
46. Anacardium/
47. Corylus/
48. Macadamia/
49. wheat.ab,ti.
50. Triticum/
51. soya.ab,ti.
52. Soybeans/
53. gluten$.ab,ti.
54. Glutens/
55. fish.ab,ti.
56. Fishes/
57. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. allerg$.ab,ti.
59. asthma$.ab,ti.
60. wheeze.ab,ti.
61. wheezing.ab,ti.
62. bronchial hyperresponsiveness.ab,ti.
63. bronchial hyperreactivity.ab,ti.
64. Forced expiratory volume.ab,ti.
65. FEV1.ab,ti.
66. "FEV 1".ab,ti.
67. "FEV0.5".ab,ti.
68. "FEV 0.5".ab,ti.
69. Forced vital capacity.ab,ti.
70. FVC.ab,ti.
71. Peak expiratory flow rate.ab,ti.
72. PEFR.ab,ti.
73. eczema.ab,ti.
74. neurodermatitis.ab,ti.
75. rhinitis.ab,ti.
76. besniers prurigo.ab,ti.
77. rhinoconjunctivitis.ab,ti.
78. hayfever.ab,ti.
79. (hay adj fever).ab,ti.
80. poll?nosis.ab,ti.
81. SAR.ab,ti.
82. (pollen adj allergy).ab,ti.
83. conjunctivitis.ab,ti.
84. immunoglobulin e.ab,ti.
85. Total IgE.ab,ti.
86. autoimmune disease?.ab,ti.
87. diabetes.ab,ti.
88. diabetic.ab,ti.
89. type 1.ab,ti.

90. c?eliac disease.ab,ti.
91. crohn$ disease.ab,ti.
92. Inflammatory Bowel Disease?.ab,ti.
93. Ulcerative colitis.ab,ti.
94. (Lympho$ adj3 thyroiditi$).ab,ti.
95. (Thyroiditi$ adj3 autoimmune).ab,ti.
96. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
97. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
98. Graves? disease.ab,ti.
99. Basedow$ disease.ab,ti.
100. exophthalmic goiter?.ab,ti.
101. (Still? Disease adj3 (juvenile or onset)).ab,ti.
102. (Juvenile adj3 arthriti$).ab,ti.
103. vitiligo.ab,ti.
104. Psorias?s.ab,ti.
105. (Arthriti? adj3 Psoria$).ab,ti.
106. atopic disease.ab,ti.
107. atopic dermatitis.ab,ti.
108. (food? adj3 sensiti$).ab,ti.
109. (food? adj3 toleran$).ab,ti.
110. (food? adj3 intoleran$).ab,ti.
111. ((aero or air$) adj3 allergen?).ab,ti.
112. (aeroallergen? adj3 sensiti$).ab,ti.
113. (allergen? adj3 sensiti$).ab,ti.
114. skin prick test$.ab,ti.
115. atopy.ab,ti.
116. hypersensitiv$.ab,ti.
117. Hypersensitivity/
118. exp Food Hypersensitivity/
119. Respiratory Hypersensitivity/
120. Asthma/
121. Bronchial Hyperreactivity/
122. Forced Expiratory Volume/
123. Vital Capacity/
124. Peak Expiratory Flow Rate/
125. Eczema/
126. Neurodermatitis/
127. Rhinitis/
128. Rhinitis, Allergic, Perennial/
129. Rhinitis, Allergic, Seasonal/
130. Conjunctivitis/
131. Immunoglobulin E/
132. Autoimmune Diseases/
133. Diabetes Mellitus, Type 1/
134. Coeliac Disease/
135. Crohn Disease/
136. Inflammatory Bowel Diseases/
137. Colitis, Ulcerative/
138. Thyroiditis, Autoimmune/

139. Hashimoto Disease/
140. Postpartum Thyroiditis/
141. Graves Disease/
142. Arthritis, Juvenile Rheumatoid/
143. Vitiligo/
144. Psoriasis/
145. Arthritis, Psoriatic/
146. Dermatitis, Atopic/
147. Hypersensitivity, Immediate/
148. 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
149. infant?.ab,ti.
150. ((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.
151. ((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.
152. 150 or 151
153. (old or age?).ab,ti.
154. 152 and 153
155. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
156. ((first or second or two) adj3 "year? of life").ab,ti.
157. Infant/
158. Infant, Newborn/
159. 149 or 154 or 155 or 156 or 157 or 158
160. clinical trial?.mp.
161. random$.mp.
162. factorial$.mp.
163. crossover$.mp.
164. placebo$.mp.
165. (doubl$ adj blind$).mp.
166. (singl$ adj blind$).mp.
167. assign$.mp.
168. volunteer$.mp.
169. cohort stud$.mp.
170. longitudinal$.mp.
171. follow-up.mp.
172. prospectiv$.mp.
173. retrospectiv$.mp.
174. case control.mp.
175. case referent.mp.
176. exp clinical trial/

177. Cross-Over Studies/
178. Placebos/
179. Double-Blind Method/
180. Single-Blind Method/
181. exp Cohort Studies/
182. case-control studies/
183. 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
184. 57 and 148 and 159 and 183

2.2. Embase

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

48. Corylus avellana/
49. Macadamia/
50. wheat.ti,ab.
51. exp wheat/
52. soya.ti,ab.
53. soybean/
54. gluten$.ti,ab.
55. gluten/
56. fish$.ti,ab.
57. fish/
58. 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
59. allerg$.ab,ti.
60. asthma$.ab,ti.
61. wheeze.ab,ti.
62. wheezing.ab,ti.
63. bronchial hyperresponsiveness.ab,ti.
64. bronchial hyperreactivity.ab,ti.
65. Forced expiratory volume.ab,ti.
66. FEV1.ab,ti.
67. "FEV 1".ab,ti.
68. "FEV0.5".ab,ti.
69. "FEV 0.5".ab,ti.
70. Forced vital capacity.ab,ti.
71. FVC.ab,ti.
72. Peak expiratory flow rate.ab,ti.
73. PEFR.ab,ti.
74. eczema.ab,ti.
75. neurodermatitis.ab,ti.
76. rhinitis.ab,ti.
77. besniers prurigo.ab,ti.
78. rhinoconjunctivitis.ab,ti.
79. hayfever.ab,ti.
80. (hay adj fever).ab,ti.
81. poll?nosis.ab,ti.
82. SAR.ab,ti.
83. (pollen adj allergy).ab,ti.
84. conjunctivitis.ab,ti.
85. immunoglobulin e.ab,ti.
86. Total IgE.ab,ti.
87. autoimmune disease?.ab,ti.
88. diabetes.ab,ti.
89. diabetic.ab,ti.
90. type 1.ab,ti.
91. c?eliac disease.ab,ti.
92. crohn$ disease.ab,ti.
93. Inflammatory Bowel Disease?.ab,ti.

94. Ulcerative colitis.ab,ti.
95. (Lympho$ adj3 thyroiditi$).ab,ti.
96. (Thyroiditi$ adj3 autoimmune).ab,ti.
97. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
98. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
99. Graves? disease.ab,ti.
100. Basedow$ disease.ab,ti.
101. exophthalmic goiter?.ab,ti.
102. (Still? Disease adj3 (juvenile or onset)).ab,ti.
103. (Juvenile adj3 arthriti$).ab,ti.
104. vitiligo.ab,ti.
105. Psorias?s.ab,ti.
106. (Arthriti? adj3 Psoria$).ab,ti.
107. atopic disease.ab,ti.
108. atopic dermatitis.ab,ti.
109. (food? adj3 sensiti$).ab,ti.
110. (food? adj3 toleran$).ab,ti.
111. (food? adj3 intoleran$).ab,ti.
112. ((aero or air$) adj3 allergen?).ab,ti.
113. (aeroallergen? adj3 sensiti$).ab,ti.
114. (allergen? adj3 sensiti$).ab,ti.
115. skin prick test$.ab,ti.
116. atopy.ab,ti.
117. hypersensitiv$.ab,ti.
118. exp hypersensitivity/
119. respiratory tract allergy/
120. asthma/
121. wheezing/
122. bronchus hyperreactivity/
123. forced expiratory volume/
124. forced vital capacity/
125. peak expiratory flow/
126. eczema/
127. neurodermatitis/
128. rhinitis/
129. rhinoconjunctivitis/
130. hay fever/
131. pollen allergy/
132. perennial rhinitis/
133. conjunctivitis/
134. immunoglobulin E/
135. autoimmune disease/
136. diabetes mellitus/
137. insulin dependent diabetes mellitus/
138. coeliac disease/
139. Crohn disease/
140. enteritis/
141. ulcerative colitis/
142. autoimmune thyroiditis/

143. Hashimoto disease/
144. postpartum thyroiditis/
145. Graves disease/
146. juvenile rheumatoid arthritis/
147. vitiligo/
148. psoriasis/
149. psoriatic arthritis/
150. atopic dermatitis/
151. nutritional intolerance/
152. 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
153. infant?.ab,ti.
154. ((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.
155. ((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.
156. 154 or 155
157. (old or age?).ab,ti.
158. 156 and 157
159. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
160. ((first or second or two) adj3 "year? of life").ab,ti.
161. infant/
162. newborn/
163. 153 or 158 or 159 or 160 or 161 or 162
164. clinical trial?.mp.
165. random$.mp.
166. factorial$.mp.
167. crossover$.mp.
168. placebo$.mp.
169. (doubl$ adj blind$).mp.
170. (singl$ adj blind$).mp.
171. assign$.mp.
172. volunteer$.mp.
173. cohort stud$.mp.
174. longitudinal$.mp.
175. follow-up.mp.
176. prospectiv$.mp.
177. retrospectiv$.mp.
178. case control.mp.
179. case referent.mp.
180. exp clinical trial/

181. crossover procedure/
182. placebo/
183. double blind procedure/
184. single blind procedure/
185. cohort analysis/
186. longitudinal study/
187. follow up/
188. prospective study/
189. retrospective study/
190. exp case control study/
191. 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
192. 58 and 152 and 163 and 191

2.3. LILACS

(tw:((complementary food*) or (introduc* food*) or wean* or solid* or semi-solid* or (baby food*) or (breast feeding) or breastfeeding or (breast fed) or breastfed or formula* or hydrolysed or bottlefed or (bottle fed) or (bottle feed*) or liquid* or milk or egg* or nut* or peanut* or almond* or (brazil* nut*) or walnut* or pecan* or pistachio* or cashew* or hazelnut* or macadamia* or wheat or soya or gluten* or fish*)
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")

2.4. COCHRANE Library

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

47. MeSH descriptor [Corylus] this term only
48. MeSH descriptor [Macadamia] this term only
49. wheat:ab,ti
50. MeSH descriptor [Triticum] this term only
51. soya:ab,ti
52. MeSH descriptor [Soybeans] this term only
53. gluten*:ab,ti
54. MeSH descriptor [Glutens] this term only
55. fish:ab,ti
56. MeSH descriptor [Fishes] this term only
57. 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
58. allerg*:ab,ti
59. asthma*:ab,ti
60. wheeze:ab,ti
61. wheezing:ab,ti
62. “bronchial hyperresponsiveness”:ab,ti
63. “bronchial hyperreactivity”:ab,ti
64. “Forced expiratory volume”:ab,ti
65. “FEV1”:ab,ti
66. "FEV 1":ab,ti
67. "FEV0.5":ab,ti
68. "FEV 0.5":ab,ti
69. “Forced vital capacity”:ab,ti
70. FVC:ab,ti
71. “Peak expiratory flow rate”:ab,ti
72. PEFR:ab,ti
73. eczema:ab,ti
74. neurodermatitis:ab,ti
75. rhinitis:ab,ti
76. “besniers prurigo”:ab,ti
77. rhinoconjunctivitis:ab,ti
78. hayfever:ab,ti
79. “hay fever”:ab,ti
80. poll*nosis:ab,ti
81. SAR:ab,ti
82. “pollen allergy”:ab,ti
83. conjunctivitis:ab,ti
84. “immunoglobulin e”:ab,ti
85. “Total IgE”:ab,ti
86. “autoimmune disease*”:ab,ti
87. diabetes:ab,ti
88. diabetic:ab,ti
89. “type 1”:ab,ti
90. “c*eliac disease”:ab,ti
91. “crohn* disease”:ab,ti
92. “Inflammatory Bowel Disease*”:ab,ti

93. “Ulcerative colitis”:ab,ti
94. (Lympho* NEAR/3 thyroiditi*):ab,ti
95. (Thyroiditi* NEAR/3 autoimmune):ab,ti
96. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
97. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
98. “Graves* disease”:ab,ti
99. “Basedow* disease”:ab,ti
100. “exophthalmic goiter*”:ab,ti
101. (Still* Disease NEAR/3 (juvenile or onset)):ab,ti
102. (Juvenile NEAR/3 arthriti*):ab,ti
103. vitiligo:ab,ti
104. Psorias*s:ab,ti
105. (Arthriti* NEAR/3 Psoria*):ab,ti
106. “atopic disease”:ab,ti
107. “atopic dermatitis”:ab,ti
108. (food* NEAR/3 sensiti*):ab,ti
109. (food* NEAR/3 toleran*):ab,ti
110. (food* NEAR/3 intoleran*):ab,ti
111. ((aero or air*) NEAR/3 allergen*):ab,ti
112. (aeroallergen* NEAR/3 sensiti*):ab,ti
113. (allergen* NEAR/3 sensiti*):ab,ti
114. “skin prick test*”:ab,ti
115. atopy:ab,ti
116. hypersensitiv*:ab,ti
117. MeSH descriptor [Hypersensitivity] this term only
118. MeSH descriptor [Food Hypersensitivity] explode all trees
119. MeSH descriptor [Respiratory Hypersensitivity] this term only
120. MeSH descriptor [Asthma] this term only
121. MeSH descriptor [Bronchial Hyperreactivity] this term only
122. MeSH descriptor [Forced Expiratory Volume] this term only
123. MeSH descriptor [Vital Capacity] this term only
124. MeSH descriptor [Peak Expiratory Flow Rate] this term only
125. MeSH descriptor [Eczema] this term only
126. MeSH descriptor [Neurodermatitis] this term only
127. MeSH descriptor [Rhinitis] this term only
128. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
129. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
130. MeSH descriptor [Conjunctivitis] this term only
131. MeSH descriptor [Immunoglobulin E] this term only
132. MeSH descriptor [Autoimmune Diseases] this term only
133. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
134. MeSH descriptor [Coeliac Disease] this term only
135. MeSH descriptor [Crohn Disease] this term only
136. MeSH descriptor [Inflammatory Bowel Diseases] this term only
137. MeSH descriptor [Colitis, Ulcerative] this term only
138. MeSH descriptor [Thyroiditis, Autoimmune] this term only
139. MeSH descriptor [Hashimoto Disease] this term only
140. MeSH descriptor [Postpartum Thyroiditis] this term only
141. MeSH descriptor [Graves Disease] this term only

142. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
143. MeSH descriptor [Vitiligo] this term only
144. MeSH descriptor [Psoriasis] this term only
145. MeSH descriptor [Arthritis, Psoriatic] this term only
146. MeSH descriptor [Dermatitis, Atopic] this term only
147. MeSH descriptor [Hypersensitivity, Immediate] this term only
148. 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
149. infant*:ab,ti
150. ((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
151. ((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
152. 150 or 151
153. (old or age*):ab,ti
154. 152 and 153
155. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
156. ((first or second or two) NEAR/3 "year* of life"):ab,ti
157. MeSH descriptor [Infant] this term only
158. MeSH descriptor [Infant, Newborn] this term only
159. 149 or 154 or 155 or 156 or 157 or 158
160. “clinical trial*”
161. random*
162. factorial*
163. crossover*
164. placebo*
165. “doubl* blind*”
166. “singl* blind*”
167. assign*
168. volunteer*
169. “cohort stud*”
170. longitudinal*
171. follow-up
172. prospectiv*
173. retrospectiv*
174. “case control”
175. “case referent”
176. MeSH descriptor [clinical trial] explode all trees
177. MeSH descriptor [Cross-Over Studies] this term only
178. MeSH descriptor [Placebos] this term only

179. MeSH descriptor [Double-Blind Method] this term only
180. MeSH descriptor [Single-Blind Method] this term only
181. MeSH descriptor [Cohort Studies] explode all trees
182. MeSH descriptor [case-control studies] this term only
183. 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
184. 57 and 148 and 159 and 183

2.5. Web of Science

1. TOPIC = (“complementary food$” or (introduc* NEAR/2 food$) or wean* or solid$ or semi-solid$ or “baby food$” or “breast feeding” or breastfeeding or “breast fed” or breastfed or formula$ or hydrolysed or bottlefed or “bottle fed” or (bottle NEAR/3 feed*) or liquid$ or milk or egg$ or nut$ or peanut$ or almond$ or (brazil$ NEAR/5 nut$) or walnut$ or pecan$ or pistachio$ or cashew$ or hazelnut$ or macadamia$ or wheat or soya or gluten* or fish*)
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"))
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