
This supplementary material has been provided by the authors to give readers additional information about their work.
Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis

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This systematic review is part of a series of systematic reviews commissioned by the UK Food Standards Agency in order to inform revisions to mother and infant feeding guidance. Together the systematic reviews evaluate the influence of maternal diet during pregnancy and lactation, and infant diet during the first year of life, on risk of allergic or autoimmune disease in the child at any time of life. The reviews 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 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 breastfeeding and timing of solid food introduction
2. REVIEW B: Timing of allergenic food introduction to the infant diet
3. REVIEW C PART I: Hydrolysed formula (recently published 1)
4. REVIEW C PART II: Other maternal and infant dietary exposures

This manuscript describes the findings of Review B.

Inclusion Criteria

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 Older systematic reviews were not included, due to the likelihood of being out of date.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 2 and extracted data from systematic reviews with revised AMSTAR score ≥32. We included other research studies published at any time prior to the search date. 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 by the study methodologists JL-B and MT), controlled clinical trials (CCT where the allocation sequence was predictable, and thought likely to lead to significant imbalance between groups in important risk factors for the outcome(s) of interest), prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies, other case control studies and cross-sectional surveys. We took a hierarchical approach to study design, such that where data were absent or limited from systematic reviews or intervention trials, we included observational study data. Where a large number of intervention trials were identified, we did not analyse data from observational studies that assessed the same intervention/exposure. We did not include non-comparative studies, or non-human studies.

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 – e.g. pregnant women with specific nutritional deficiencies or infants born prematurely (<31 weeks gestation). We did not exclude studies on the basis of including specific ethnic groups or studies of high risk infants.

Interventions/ exposures

Definition of allergenic foods: In this review, allergenic foods are defined as cow’s milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts and soybeans. 3 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 referred to gluten/wheat/cereal introduction as ‘cereal’ in the observational study reports, and as ‘wheat’ or ‘gluten’ in the intervention study reports since intervention trials more frequently used wheat/gluten, or wheat/gluten avoidance as the intervention whereas observational studies more frequently assessed gluten-containing cereal as the exposure of interest.

Definition of timing of allergenic food exposure interventions: Comparison groups for timing of allergenic food introduction in observation studies varied, therefore for data synthesis we grouped data according to age at introduction as follows: <1-4 vs. ≥1-4 months, <5-7 vs. ≥5-7 months and <8-12 vs. ≥8-12 months. For cow’s milk introduction the first category was further divided into <1-2 vs. ≥1-2 months, and <3-4 vs. ≥3-4 months.
In the intervention trials for this review we included studies comparing single brief early allergenic food exposure (typically during 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, and multiple allergenic food interventions were included in analyses pertaining to all allergenic foods used. We included intervention studies which advised either early or delayed allergenic food introduction, and 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. This means that for some analyses there is uncertainty about the directness of any associations found between intervention group and allergic/autoimmune outcomes; and for some studies there is uncertainty about the degree to which timing of allergenic food introduction differed between intervention and control groups due to poor reporting of the timing of allergenic food introduction in the control group.

Study Outcomes

We selected atopic and autoimmune outcomes on the basis of their population prevalence in children and young adults in the UK. We included diseases with a prevalence of at least 1 in 1000, in children/adolescents or young adults (aged <40 years), but did not include rarer diseases. 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 esophagitis, 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 i.e. 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 i.e. 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.

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 i.e. 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 i.e. 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 i.e 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.

5. 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. 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, Massachusetts).

Autoimmune outcomes:

1. Type I diabetes mellitus – defined as a medical diagnosis e.g. using the 1999 WHO recommendations for diagnosis and classification of diabetes mellitus \(^7\), 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. Celiac 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. Juvenile rheumatoid arthritis – defined as a medical diagnosis eg using the 2001 revised International League of Associations for Rheumatology (ILAR) classification criteria. \(^8\)

5. Vitiligo - defined as a medical diagnosis. Primary assessment: medical diagnosis using the Vitiligo European Task Force 2007 criteria or similar. \(^9\)

6. Psoriasis - defined as a medical diagnosis.

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 as either full text, letter or abstract publications 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. Where necessary we contacted the authors of eligible or potentially eligible studies to request original data or further details. The search strategies were extensively piloted and refined to optimize sensitivity, comparing search results with those of other high quality published systematic reviews. The final search strategies for this review are listed at the end of the supplemental material 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 updates. The search strategy included a sensitive search filter for retrieving systematic reviews. \(^10\) Open Grey was searched using 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 arthritis OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)’. 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 ‘milk OR nut OR wheat OR egg OR food OR diet’. The citations identified in searches were imported into Endnote libraries for de-duplication and title screening.

Study selection and data extraction

Study selection

Title and abstract screening was undertaken in duplicate by a team of 7 researchers (RB, VGL, DI, NG, KJ, JC, ZR).

Two researchers undertook title screening independently, and met to agree included and excluded titles. Their screening was checked by a third member of the team, and uncertainties were brought to a full team meeting for discussion. This procedure took place between February and April 2014, with weekly team meetings to discuss uncertainties about study eligibility, and again in 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.

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Data extraction

An Excel data extraction form was developed, piloted and refined by DI, VGL, RB and JLB – separate forms were used for intervention studies, cohort studies and case-control/cross-sectional studies. Data extraction was undertaken in duplicate by a team of 10 researchers (DI, RB, SC, VGL, JC, ZR, NG, KJ, AL, AG). Disagreements and uncertainties about data coding were discussed within the team with leads as follows - RB (clinical queries), VGLA (nutritional queries), DI (analysis and coding queries) and JLB (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 section 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.

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 JRB.

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. We defined short term early intervention trials as trials where the intervention period is during the first week of life, and does not extend beyond that time period; and longer term early intervention trials as trials where the intervention period is not restricted to the first week of life. We refer to the legume peanut (groundnut) and to tree nuts (e.g. hazelnut, almond, cashew) collectively as ‘nuts’.

Data selection for meta-analysis

All data on timing of allergenic food introduction were extracted from included 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 i.e. ‘less than’ a certain duration. 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. In general from individual studies reporting more than one measure for the same outcome, we selected data for analysis reporting time to event (hazard ratio) in preference to cumulative incidence or lifetime prevalence ie ‘disease ever’, in turn in preference to point prevalence data i.e. ‘disease in the last 12 months’ for all binary outcomes with the exception of the non-clinical outcomes allergic sensitisation and lung function, where point prevalence was analysed in preference to cumulative measures. 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 (e.g. age 1 and 3 years), we selected data for analysis within specific age groups that were most complete i.e. 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 since data for these outcomes were relatively sparse. 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. Data that could not be included in any meta-analysis, for example medians, or means without a standard deviation or standard error, or ‘no significant difference’ statements, were reported narratively. The outcomes of both meta-analysed and narratively reported studies were considered together when interpreting data and making conclusions.

Risk of bias (quality) assessment

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.

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). 11 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/cross-sectional studies respectively. 12 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, 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.

Strategy for data synthesis

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

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 of observational study data, and unadjusted data for intervention trials, where available. Random effect meta-analyses were performed to allow for heterogeneity between studies.

Heterogeneity

Heterogeneity was quantified using I². We explored reasons for heterogeneity using subgroup analyses based on study level factors. We classified heterogeneity as low (I²<25%), moderate (I² 25-50%), high (I² 50-75%) or extreme.
(I²>75%). For single study analyses, and where I² 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.

**Data analysis**

Pooled results for binary outcomes from intervention studies are presented as RR calculated from the frequencies given in the study using the Mantel-Haenszel method (with continuity correction of 0.5 in studies with zero cell frequencies) for pooled RR. Pooled results for continuous outcomes measured using similar scales are presented as mean differences with 95% confidence intervals. Where different scales are 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. For observational studies of rare outcomes (i.e. autoimmune outcomes) reporting Odds Ratios (OR) and Risk Ratios (RR) we combined OR and RR in meta-analysis and plotted as pooled OR – as the majority of cohorts, case control studies and cross sectional studies reported this effect measure – using the generic inverse variance method. This was reported separately from and Hazard Ratios (HR). For observational analysis of common outcomes (i.e. allergic outcomes) OR, RR and HR were analysed separately. Key findings from intervention trials are presented in Summary of Findings tables similar to those used by the Cochrane Collaboration.\(^1\) We conducted post hoc Trial Sequential Analysis to quantify statistical reliability of key positive review findings using 5% significance, 80% power and control event rates from included studies to estimate the optimal heterogeneity-adjusted and non-adjusted information sizes needed to identify relative risk reductions of 10%, 20% and 30%. Trial sequential analysis is a method for quantifying the statistical reliability of data in a cumulative meta-analysis, which adjusts significance levels for sparse data and repetitive testing on accumulating data. Trial sequential analysis employed the Lan–DeMets alpha-spending function using O’Brien–Fleming monitoring boundaries, as previously described.\(^14\) Statistical analyses were undertaken by DI, under supervision from JL-B, using the statistical programme (R version 3.1.0, 2014, www.r-project.org). Trial sequential analysis was undertaken by JL-B using TSA version 0.9 Beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

**Planned subgroup analyses**

We planned certain subgroup and stratified analyses prior to running our search. Subgroup analysis was undertaken for all meta-analyses with ≥ 6 studies included. We 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 presented all meta-analyses of observational data stratified for prospective versus retrospective study design. 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 allergic or autoimmune disease, versus those at normal or low risk of disease.

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.

**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 recommendations for allergenic food introduction in infants, and the prevalence of some of the outcomes, have changed over time.

**Review registration**

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42013004239; www.crd.york.ac.uk/Prospero) on the 5th August 2013, prior to title screening or selecting any studies from the search results. The protocol was revised following detailed review by the UK Food Standards Agency, the UK Scientific Advisory Committee on Nutrition, independent experts Professor Graham Devreux and Dr Carina Venter, and the Lancet peer review service, prior to being registered on PROSPERO.
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. We included TSA as an additional statistical measure of confidence in the key positive study findings.

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 (e.g. 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 certainty evidence further research is very unlikely to change our confidence in the estimate of effect; for MODERATE certainty 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 certainty 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 certainty evidence any estimate of effect is very uncertain. Further detailed explanation of GRADE can be found at:

### eTable 1. Relationship between timing of gluten introduction and celiac disease - data from the systematic review of Szajeweska et al 2012

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falth-Magnusson 1996</td>
<td>336</td>
<td>Mean age of gluten introduction in cases versus controls</td>
<td>Mean 6 months CD, 5-6 months control</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Ivarsson 2002</td>
<td>1,272</td>
<td>Gluten introduction at 1-4 compared with 5-6 months or 7-12 months</td>
<td>5-6 months OR 1.4 (0.9, 2.4); 7-12 months OR 0.8 (0.4, 1.4)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Norris 2005</td>
<td>1,560</td>
<td>Gluten introduction at 4-6 months compared with 1-3 months or ≥7 months</td>
<td>1-3 months HR 2.94 (0.83, 10.40); ≥7 months HR 1.78 (0.92, 3.42)</td>
<td>Increased risk of CD serology with early or late gluten introduction</td>
</tr>
<tr>
<td>Peters 2001</td>
<td>280</td>
<td>Gluten introduction at &lt;4 months compared with 4 months, 5 months, or &gt;5 months</td>
<td>4 months aOR 0.52 (0.18, 1.44); 5 months aOR 1.21 (0.40, 3.68); &gt;5 months aOR 0.72 (0.28, 1.85)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Welander 2010</td>
<td>9,364</td>
<td>Gluten introduction at 5-6 months compared with 0-2; 3-4; 7-8; 9-10; or 11-12 months</td>
<td>3-4 months HR 1.0 (0.3, 3.3); 7-8 months HR 1.1 (0.6, 2.0)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Ziegler 2003</td>
<td>1,610</td>
<td>Gluten introduction at 3.1-6 months compared with ≤3 months or &gt;6 months</td>
<td>≤3 months HR 2.3 (0.3, 18.2); &gt;6 months HR 0.7 (0.3, 1.8)</td>
<td>No significant difference</td>
</tr>
</tbody>
</table>

aOR adjusted odds ratio; CD celiac disease; HR hazard ratio; OR odds ratio.
Table 2. Relationship between timing of gluten introduction and celiac disease - data from systematic review of Pinto-Sanchez et al 2016

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analyses of Cohort Studies</td>
<td></td>
<td>Introduction of gluten at &lt;4 vs &gt;6 months</td>
<td>RR 1.08 (0.76, 1.54) $I^2$=0%</td>
<td>No significant difference</td>
</tr>
<tr>
<td>4 studies</td>
<td>50,351</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 studies</td>
<td>100,224</td>
<td>Introduction of gluten at &lt;4 vs 4-6 months</td>
<td>RR 1.27; (0.86, 1.86) $I^2$=3%</td>
<td>No significant difference</td>
</tr>
<tr>
<td>4 studies</td>
<td>774</td>
<td>Introduction of gluten at &gt;6 vs 4-6 months</td>
<td>RR 1.25 (1.08-1.45) $I^2$=0%</td>
<td>Increased risk with later introduction of gluten</td>
</tr>
<tr>
<td>5 studies</td>
<td>48,845</td>
<td>Difference in timing of gluten introduction in CD versus controls</td>
<td>Mean difference (months) -0.10 (-0.27, 0.07) $I^2$= 12%</td>
<td>No significant difference</td>
</tr>
<tr>
<td>5 studies</td>
<td>48,845</td>
<td>Breastfeeding at the time of gluten introduction</td>
<td>$^a$OR 0.70 (0.45, 1.10) $I^2$=78%</td>
<td>No significant difference</td>
</tr>
</tbody>
</table>

Other data from the systematic review of Pinto-Sanchez, which overall included data from 13 observational studies (5 cohort studies) did not identify evidence for a relationship between timing of gluten introduction and risk of CD. $^a$Within this analysis the prospective cohort studies of Stordal 2013 and Norris 2005 showed no evidence for association; but 3 of 4 case control studies found significantly reduced breastfeeding at the time of gluten introduction in CD compared with controls.
**eTable 3. Characteristics of studies examining timing of food introduction and risk of allergic diseases (24 intervention studies)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. in Intervention Group</th>
<th>No. in Control Group</th>
<th>Intervention</th>
<th>Population</th>
<th>Country</th>
<th>aDisease risk</th>
<th>bAge (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellach, 2015&lt;sup&gt;23&lt;/sup&gt;</td>
<td>RCT</td>
<td>184</td>
<td>199</td>
<td>Pasteurised egg white powder (2.5 g protein) versus rice powder 3 times per week from 4-6 months to 12 months</td>
<td>HEAP Study: Infants aged 4-6 months with specific IgE to egg &lt;0.35 kU/L</td>
<td>Germany</td>
<td>Normal</td>
<td>1</td>
<td>AS (sIgE-Egg); FA (OFC)</td>
</tr>
<tr>
<td>Becker, 2004&lt;sup&gt;24&lt;/sup&gt;; Chan-Yeung, 2000/5&lt;sup&gt;25, 26&lt;/sup&gt;; Carlsten 2013&lt;sup&gt;27&lt;/sup&gt;</td>
<td>RCT</td>
<td>268</td>
<td>281</td>
<td>MULTIFACETED. Standard care versus BF ≥4 months, allergenic food exclusion during pregnancy and lactation, delayed solid (≥6 months) and allergenic food (milk, seafood, peanut ≥12 months) and environmental control</td>
<td>CAPPS (Canadian Asthma Primary Prevention study): Children with family history of atopic disease</td>
<td>Canada</td>
<td>High</td>
<td>7</td>
<td>Allergic rhinitis (DD); Eczema (physician assessment); Wheeze (ISAAC and modified ECRHS); BHR (PC20 &lt;7.8mg/ml); Lung function (FEV&lt;sub&gt;1&lt;/sub&gt;); AS (SPT-aero; SPT-CM; SPT-Egg; SPT-Peanut)</td>
</tr>
<tr>
<td>Brown, 1969&lt;sup&gt;28&lt;/sup&gt;</td>
<td>RCT</td>
<td>196</td>
<td>183</td>
<td>Cow’s milk versus soya based diet as needed, from birth until introduction of complementary foods. 46% in control group introduced cow’s milk, versus 95% in cow’s milk group</td>
<td>MONTEFIORE Study: Mothers in a Health Insurance Plan in Greater New York</td>
<td>USA</td>
<td>Normal</td>
<td>2</td>
<td>Allergic rhinitis (DD); Eczema (physician assessment)</td>
</tr>
<tr>
<td>Burr, 1993&lt;sup&gt;29&lt;/sup&gt;; Merrett, 1988&lt;sup&gt;30&lt;/sup&gt;; Miskelly, 1988&lt;sup&gt;31&lt;/sup&gt;</td>
<td>RCT</td>
<td>238</td>
<td>249</td>
<td>Cow’s milk versus soya formula as needed from birth to 6 months. Milk intake restricted during pregnancy &amp; lactation in soya group</td>
<td>Infants recruited in South Wales with history of asthma, eczema or hayfever in at least one family member</td>
<td>UK</td>
<td>High</td>
<td>1, 7</td>
<td>Allergic rhinitis (parental report); Eczema (physician assessment or parent report); AS (SPT-Any)</td>
</tr>
<tr>
<td>de Jong, 2002&lt;sup&gt;32&lt;/sup&gt;</td>
<td>RCT</td>
<td>758</td>
<td>775</td>
<td>Cow’s milk formula ≥3 times in the first 3 days, versus protein-free placebo formula</td>
<td>BOKAAL Study: Healthy term newborns whose mother intended to breastfeeding for ≥6 weeks</td>
<td>Netherland</td>
<td>Normal</td>
<td>5</td>
<td>Allergic rhinitis (DD); Eczema (ISAAC); Wheeze (parent reported); AS (sIgE-Any; sIgE-CM; sIgE-Egg)</td>
</tr>
</tbody>
</table>
### eTable 3. Characteristics of studies examining timing of food introduction and risk of allergic diseases (24 intervention studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. in Intervention Group</th>
<th>No. in Control Group</th>
<th>Intervention</th>
<th>Population</th>
<th>Country</th>
<th>Disease risk</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du Toit, 2016 33,34</td>
<td>RCT</td>
<td>319</td>
<td>321</td>
<td>6g peanut protein per week, divided between 3 meals, from 4-11 months to 5 years, versus peanut avoidance</td>
<td>LEAP (Learning Early About Peanut allergy) Study: Infants aged 4-11 months with moderate or severe eczema or egg allergy, and peanut SPT &lt;4mm. Mean 7.8 months</td>
<td>UK</td>
<td>High</td>
<td>5, 6</td>
<td>Allergic rhinitis (parental report); Wheeze (physician assessment); AS (sIgE and SPT to Peanut); FA (OFC)</td>
</tr>
<tr>
<td>Halmerbauer, 2002 and 2003 35,36</td>
<td>RCT</td>
<td>347</td>
<td>349</td>
<td>MULTIFACETED. Standard care versus e BF ≥ 3 months, delayed solid (≥6 months) and allergenic food (milk, egg, fish, nuts ≥1 year), and environmental control</td>
<td>SPACE (Study on the Prevention of Allergy in Children in Europe): ≥1 parent with a positive allergy history plus aeroallergen sensitisation</td>
<td>UK, Germany, Austria</td>
<td>High</td>
<td>1</td>
<td>Eczema (DD); Wheeze (parent reported wheeze ever; ≥3 episodes of wheeze); AS (sIgE and SPT to any Allergen, CM and Egg); FA (DD)</td>
</tr>
<tr>
<td>Hide, 1994 and 1996 37,38</td>
<td>RCT</td>
<td>68</td>
<td>71</td>
<td>MULTIFACETED. Standard care versus cow’s milk, egg, wheat, nuts, fish and soya excluded from diet of infant and lactating mother to 9 months, soya hydrolysate if needed, environmental control</td>
<td>Isle of Wight Study: Infants with a first degree relative affected by an allergic disorder plus cord blood IgE&gt;O.5kU/L</td>
<td>UK</td>
<td>High</td>
<td>1, 8, 18</td>
<td>Allergic rhinitis (DD); Eczema (ISAAC); Wheeze; Recurrent wheeze (≥3 episodes), BHR (PC20&lt;8mg/ml); AS (SPT-CM; SPT-Egg, Total IgE); FA (parental report or OFC)</td>
</tr>
<tr>
<td>Arshad, 1992, 2003 and 2007 39,41 Scott, 2012 42</td>
<td>RCT</td>
<td>120</td>
<td>115</td>
<td>Cow's milk formula as needed during first 9 months, versus soya formula and egg avoidance to 9 months</td>
<td></td>
<td>USA</td>
<td>High</td>
<td>10</td>
<td>Allergic rhinitis (DD); Eczema (physician assessment); Wheeze (DD)</td>
</tr>
<tr>
<td>Johnston e, 1966 43</td>
<td>RCT</td>
<td>25</td>
<td>23</td>
<td>Cow's milk versus soya formula as needed until 9 months. Study formula introduced at median 1.5 months age</td>
<td>Infants with biparental history of atopic disease</td>
<td>Sweden</td>
<td>High</td>
<td>4</td>
<td>Allergic rhinitis, Wheeze (DD); Eczema (physician assessment); AS (SPT-any; sIgE-CM, Total IgE)</td>
</tr>
</tbody>
</table>

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<th>Study</th>
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<th>No. in Intervention Group</th>
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<th>Population</th>
<th>Country</th>
<th>(^a)Disease risk</th>
<th>(^b)Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowe, 2011</td>
<td>RCT</td>
<td>206</td>
<td>208</td>
<td>Cow's milk versus soya formula, as needed from birth. Introduced at median 4 months</td>
<td>Melbourne Atopy Cohort Study (MACS): Infants with a first degree relative with eczema, asthma, AR or food allergy</td>
<td>Australia</td>
<td>High</td>
<td>7</td>
<td>Allergic rhinitis, Wheeze (DD); Eczema (DD); AS (SPT-Any, SPT-CM); FA (physician assessment)</td>
</tr>
<tr>
<td>Matthew, 1977</td>
<td>RCT</td>
<td>35</td>
<td>27</td>
<td>MULTIFACETED. Standard care in cow's milk formula fed infants, versus BF for ≥6 months, soya in place of cow's milk, delayed solid (≥3 months) and allergenic (cow's milk, fish and egg ≥6 months), environmental control</td>
<td>Included mothers with a convincing history of asthma, AR, and eczema from Queen Charlotte's Hospital</td>
<td>UK</td>
<td>High</td>
<td>1</td>
<td>Eczema (DD)</td>
</tr>
<tr>
<td>Natsume, 2016</td>
<td>RCT</td>
<td>60</td>
<td>61</td>
<td>Heated egg powder (50mg daily from 6-9 months; 250mg daily from 9-12 months) versus placebo from 6 to 12 months</td>
<td>Infants with atopic dermatitis by 4-5 months</td>
<td>Japan</td>
<td>High</td>
<td>1</td>
<td>OFC</td>
</tr>
<tr>
<td>Palmer, 2013</td>
<td>RCT</td>
<td>49</td>
<td>37</td>
<td>1 teaspoon per day of pasteurized raw whole egg powder, versus rice flour powder, given daily from randomization at 4 months to 8 months age</td>
<td>Singleton term infants with symptoms of moderate-to-severe eczema.</td>
<td>Australia</td>
<td>High</td>
<td>1</td>
<td>AS (SPT or sIgE to Egg); FA (OFC)</td>
</tr>
<tr>
<td>Perkin, 2016</td>
<td>RCT</td>
<td>652</td>
<td>651</td>
<td>Sequential introduction of six allergenic foods - cow’s milk, peanut, egg, wheat, sesame and fish from age 3 months, versus avoidance to ≥6 months</td>
<td>Enquiring about tolerance (EAT) Study: Children exclusively breastfed at 3 months and gestation over 37 weeks.</td>
<td>UK</td>
<td>Normal</td>
<td>3</td>
<td>Wheeze (parent-reported wheeze ever; ≥4 episodes of wheeze); AS (SPT-Food; SPT-CM; SPT-Egg; SPT-Peanut); FA (OFC)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>No. in Intervention Group</td>
<td>No. in Control Group</td>
<td>Intervention</td>
<td>Population</td>
<td>Country</td>
<td>Disease risk</td>
<td>Age (yrs)</td>
<td>Outcomes reported</td>
</tr>
<tr>
<td>-------------</td>
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<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
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<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Shao, 2006</td>
<td>RCT</td>
<td>23</td>
<td>23</td>
<td>MULTIFACETED. Standard advice versus eBF for 4 months, allergic food exclusion during lactation, delayed solid (4 months) and allergenic food (fish and prawn ≥6 months; egg and nuts ≥12 months), pHF if necessary</td>
<td>Chinese babies with parental history of allergic disease, with specific food allergies according to +SPT</td>
<td>China</td>
<td>High</td>
<td>1.5</td>
<td>Eczema (unclear); AS (sIgE or SPT-any)</td>
</tr>
<tr>
<td>Tan, 2016</td>
<td>RCT</td>
<td>165</td>
<td>154</td>
<td>Pasteurised whole egg powder (350mg egg protein) daily versus rice powder from the time of solid food introduction until 8 months age</td>
<td>BEAT Study: Infants with a first degree relative with allergic disease, and egg SPT &lt;2mm at age 4 months.</td>
<td>Australia</td>
<td>High</td>
<td>1</td>
<td>AS (SPT-Egg); FA (OFC)</td>
</tr>
<tr>
<td>Zeiger, 1989, 1992 and 1994</td>
<td>RCT</td>
<td>~185</td>
<td>~103</td>
<td>MULTIFACETED. Standard care versus infants cow’s milk, wheat, soy, egg, peanut and fish avoidance to ≥1 year &amp; maternal allergenic food avoidance during pregnancy and lactation</td>
<td>Infants covered by Kaiser Permanente Health Plan, with an allergic parent.</td>
<td>USA</td>
<td>High</td>
<td>2, 4, 7</td>
<td>Allergic rhinitis (parental report); Eczema (physician assessment); Wheeze (≥2 episodes of physician diagnosed wheeze); AS (SPT-Aero); FA (DD)</td>
</tr>
<tr>
<td>Zhou, 2014</td>
<td>RCT</td>
<td>99</td>
<td>101</td>
<td>Cow’s milk versus goat milk formula from &lt;2 weeks age</td>
<td>Healthy term infants fully formula fed within 2 weeks of birth.</td>
<td>Australia</td>
<td>Normal</td>
<td>1</td>
<td>Eczema (method unclear. Severity assessed using SCORAD); FA (medically diagnosed food allergy – not otherwise defined)</td>
</tr>
</tbody>
</table>
## eTable 3. Characteristics of studies examining timing of food introduction and risk of allergic diseases (24 intervention studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. in Intervention Group</th>
<th>No. in Control Group</th>
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<th>Population</th>
<th>Country</th>
<th>aDisease risk</th>
<th>bAge (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruskay, 1982</td>
<td>CCT</td>
<td>249</td>
<td>79</td>
<td>Cow's milk formula versus soya formula as needed, from birth to 9 months. Introduced at median 5 month</td>
<td>Infants with a positive family history of allergy, fed a formula milk from &lt;4 months age.</td>
<td>USA</td>
<td>High</td>
<td>3, 5</td>
<td>Allergic rhinitis (DD); eczema (physician assessment); wheeze (physician assessment)</td>
</tr>
<tr>
<td>Halpern, 1973</td>
<td>CCT</td>
<td>~359 CM</td>
<td>~359 Soya</td>
<td>Allocated by paediatrician at birth to feed by breast, cow's milk or soya milk.</td>
<td>Caucasian infants with a family history of allergic disease.</td>
<td>USA</td>
<td>High</td>
<td>5</td>
<td>Allergic rhinitis (physician assessment); eczema (physician assessment); Wheeze (physician assessment); FA (OFC)</td>
</tr>
<tr>
<td>Lindfors, 1988</td>
<td>CCT</td>
<td>112</td>
<td>104</td>
<td>Cow's milk formula given as first meal and increased to ≤60 ml every 4 hours, until breastfeeding started; versus breastfed from birth.</td>
<td>Healthy low birth weight infants with gestational age 37-42 weeks.</td>
<td>Sweden</td>
<td>Normal</td>
<td>1.5, 5</td>
<td>Allergic rhinitis (DD); eczema (physician assessment); Wheeze (physician assessment)</td>
</tr>
<tr>
<td>Lindfors, 1992</td>
<td>CCT</td>
<td>112</td>
<td>104</td>
<td>Cow's milk formula given as first meal and increased to ≤60 ml every 4 hours, until breastfeeding started; versus breastfed from birth.</td>
<td>Healthy low birth weight infants with gestational age 37-42 weeks.</td>
<td>Sweden</td>
<td>Normal</td>
<td>1.5, 5</td>
<td>Allergic rhinitis (DD); eczema (physician assessment); Wheeze (physician assessment)</td>
</tr>
<tr>
<td>Juvonen, 1996</td>
<td>qRCT</td>
<td>~43</td>
<td>~58</td>
<td>Cow's milk formula versus breast milk for first 3 days of life.</td>
<td>Healthy term infants</td>
<td>Sweden</td>
<td>Normal</td>
<td>3</td>
<td>Eczema, Wheeze, FA (physician assessment); AS (Total IgE, sIgE-CM, sIgE-Egg)</td>
</tr>
<tr>
<td>Saarinen, 2000</td>
<td>qRCT</td>
<td>1789</td>
<td>1859</td>
<td>Cow's milk formula versus pasteurised human milk from birth for mean 4 days.</td>
<td>Term infants in Helsinki fed formula milk before hospital discharge</td>
<td>Finland</td>
<td>normal</td>
<td>2</td>
<td>FA CM (OFC)</td>
</tr>
</tbody>
</table>

RCT randomised controlled trial; CCT case-control trial; qRCT quasi randomised controlled trial; AS allergic sensitisation; OFC oral food challenge; FA food allergy; DD doctor diagnosis; BF breastfeeding; eBF exclusive breastfeeding; pHF partially hydrolysed formula; ISAAC International Study of Asthma and Allergies in Children; ECRHS European Community Respiratory Health Survey; BHR bronchial hyper responsiveness; FEV1 forced expiratory volume in 1 second; FVC forced vital capacity; PC 20% provocative concentration of methacholine resulting in 20% fall in FEV1; SPT skin prick test; SPT-any SPT to any food; CM cow’s milk; sIgE specific IgE; SCORAD scoring atopic dermatitis; I Interview; Q Questionnaire; R Records. Multiple references for a single study refer to multiple publications from the same trial. aDisease risk is high where the population studied were at high inherited risk of allergic disease. bAge at outcome – for some studies outcome data used in the systematic review were derived from evaluations at multiple ages.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Country</th>
<th>Population</th>
<th>Exposure(s)</th>
<th>Measure</th>
<th>*Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alm, 2008</td>
<td>PC</td>
<td>4941</td>
<td>Sweden</td>
<td><strong>Infants of Western Sweden:</strong> Population based birth cohort of infants born in the region in 2003</td>
<td>Cow’s milk, fish, egg, cereal</td>
<td>Questionnaire</td>
<td>1, 4</td>
<td>Eczema (parent reported); Allergic rhinitis (parent report or DD); AS (SPT or IgE aero)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Businco,</td>
<td>PC</td>
<td>101</td>
<td>Italy</td>
<td>Infants of atopic parents recruited at birth in a hospital in Rome, Italy between 1985 and 1988</td>
<td>Cow’s milk, and soya</td>
<td>Interview</td>
<td>2</td>
<td>Allergic rhinitis, Eczema, Wheeze (physician assessment plus parent reported); AS (Total-IgE); FA (history of reaction to food)</td>
</tr>
<tr>
<td>1993;</td>
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<td>Businco,</td>
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<td>1995</td>
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</tr>
<tr>
<td>Cogswell,</td>
<td>PC</td>
<td>73</td>
<td>UK</td>
<td>Babies of parent with a history of hay fever or asthma born in the maternity department of a district general hospital</td>
<td>Cow’s milk</td>
<td>Diary</td>
<td>5</td>
<td>Eczema (physician assessment plus sensitisation); AS (SPT-any)</td>
</tr>
<tr>
<td>1987</td>
<td></td>
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</tr>
<tr>
<td>Dunlop,</td>
<td>PC</td>
<td>1326</td>
<td>Slovakia</td>
<td><strong>Slovak birth cohort:</strong> The 1st 250 pregnant women delivering at maternity hospitals in the selected study sites were recruited between 1997 and 1999</td>
<td>Cow’s milk, fish, egg, nuts</td>
<td>Questionnaire</td>
<td>1</td>
<td>Eczema (physician assessment)</td>
</tr>
<tr>
<td>2006</td>
<td></td>
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<tr>
<td>Epstein</td>
<td>PC</td>
<td>636</td>
<td>USA</td>
<td><strong>CCAAPS:</strong> Newborns at high risk of allergy were identified in the Cincinnati metropolitan area, US by public birth records from 2001 to 2003</td>
<td>Egg, nuts</td>
<td>Questionnaire</td>
<td>4</td>
<td>Eczema (parent reported (sensitivity analysis with physician assessment))</td>
</tr>
<tr>
<td>2011</td>
<td></td>
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<tr>
<td>Fergusson,</td>
<td>PC</td>
<td>1175</td>
<td>New Zealand</td>
<td><strong>Christchurch Child Development Study:</strong> A cohort of children born in the Christchurch urban region New Zealand during mid-1977</td>
<td>Cow’s milk, egg, cereal</td>
<td>Records, diary and questionnaire</td>
<td>1, 2, 4, 6, 10</td>
<td>Eczema (DD); Wheeze (DD or medical records and Q)</td>
</tr>
<tr>
<td>1981;</td>
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<td>Horwood,</td>
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</tr>
</tbody>
</table>

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eTable 4. Characteristics of studies examining timing of food introduction and risk of allergic diseases (69 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Country</th>
<th>Population</th>
<th>Exposure(s)</th>
<th>Measure</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goksor, 2009</td>
<td>PC</td>
<td>5654</td>
<td>Sweden</td>
<td>West of Sweden cohort: urban, rural and coastal areas in Western Sweden, ~60% with atopic heredity</td>
<td>Gluten, egg and fish</td>
<td>Questionnaire</td>
<td>4.5, 8</td>
<td>Wheeze (ISAAC Q)</td>
</tr>
<tr>
<td>(Goksor, 2013)</td>
<td></td>
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<tr>
<td>(Zutavern, 2004)</td>
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<tr>
<td>Harris, 2001</td>
<td>PC</td>
<td>622</td>
<td>UK</td>
<td>Population based birth cohort of newly pregnant women who presented at one of three general practices in Ashford, Kent UK between 1993 and 1995</td>
<td>Cow’s milk, cereal, rice, fish, egg</td>
<td>Questionnaire</td>
<td>2, 5, 5</td>
<td>Eczema (DD); Wheeze (parent report); AS (SPT aero)</td>
</tr>
<tr>
<td>(Zutavern, 2004)</td>
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</tr>
<tr>
<td>Hesselmar, 2010</td>
<td>PC</td>
<td>184</td>
<td>Sweden</td>
<td>ALLERGYFLORA: Birth cohort in Sweden enriched with children with family history of allergies</td>
<td>Cow’s milk, egg, fish</td>
<td>Interview and questionnaire</td>
<td>1.5</td>
<td>Eczema (physician assessment, and full-filling Williams’ criteria); Wheeze (physician assessment (≥3 episodes of wheeze in the last 1.5 year); AS (sIgE-food); FA (physician assessment plus open food challenge)</td>
</tr>
<tr>
<td>Joseph, 2011</td>
<td>PC</td>
<td>594</td>
<td>USA</td>
<td>WHEALS: Population based birth cohort with pregnant woman recruited from prenatal care in Henry Ford Hospital obstetric clinics between 2003 and 2007 in Detroit area</td>
<td>Cow’s milk (part of a ‘complementary food’ definition)</td>
<td>Interview</td>
<td>2-3</td>
<td>AS (sIgE egg, sIgE cow’s milk, sIgE peanut)</td>
</tr>
<tr>
<td>Katz, 2010</td>
<td>PC</td>
<td>1270</td>
<td>Israel</td>
<td>Population based birth cohort of all newborns born between 2004 and 2006, at the Assaf-Harofeh Hospital in Zerifin</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>1</td>
<td>FA (parent reported plus sensitisation followed by oral food challenge)</td>
</tr>
<tr>
<td>Katz, 2010</td>
<td>PC</td>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>Kemeny, 1991</td>
<td>PC</td>
<td>180</td>
<td>UK</td>
<td>Population based birth cohort of infants born at Dulwich and King’s College Hospitals in London</td>
<td>Cow’s milk</td>
<td>Unclear</td>
<td>1</td>
<td>Eczema (unclear); Wheeze (parent report of symptoms); AS (SPT cow’s milk, SPT egg); FA (history of reaction to food)</td>
</tr>
</tbody>
</table>
eTable 4. Characteristics of studies examining timing of food introduction and risk of allergic diseases (69 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
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<th>Population</th>
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<th>Measure</th>
<th>*Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiefte-de Jong, 2012 85; Tromp, 2011 86</td>
<td>PC</td>
<td>7210</td>
<td>Netherlands</td>
<td>GENERATION R: Population based birth cohort with pregnant women recruited &lt; 25 weeks gestation in Rotterdam</td>
<td>Cow’s milk, soya, egg, peanut, fish, gluten</td>
<td>Questionnaire 2, 3, 4</td>
<td></td>
<td>Wheeze (parent report (ISAAC Q); DD)</td>
</tr>
<tr>
<td>Koplin, 2008 87</td>
<td>PC</td>
<td>449</td>
<td>Australia</td>
<td>Members of MACS, aRCT of the effect of 3 infant formulas in a cohort of children with a family history of allergy born between 1990 and 1994 whose mothers were recruited during pregnancy</td>
<td>Soya</td>
<td>Interview and Questionnaire 2</td>
<td></td>
<td>AS (SPT peanut)</td>
</tr>
<tr>
<td>Koplin, 2010 88, Koplin, 2012 89</td>
<td>PC</td>
<td>699</td>
<td>Australia</td>
<td>HealthNUTS study: 11-15 months old infants were recruited as they attended 131 council-run immunization sessions across Melbourne between June 2008 and January 2010</td>
<td>Egg</td>
<td>Interview and Questionnaire 1</td>
<td></td>
<td>FA (sensitisation plus open food challenge)</td>
</tr>
<tr>
<td>Kull, 2006 90</td>
<td>PC</td>
<td>3230</td>
<td>Sweden</td>
<td>BAMSE: Prospective birth cohort of newborns in a predefined area of Stockholm, Sweden between 1994 and 1997</td>
<td>Fish</td>
<td>Questionnaire 4</td>
<td></td>
<td>Allergic rhinitis (DD or parent report); eczema (DD or dry skin with itchy rash for &gt;= 2 weeks); Wheeze (&gt;= 3 episodes of wheeze in the last 12 months OR wheeze plus ICS); AS (sIgE any)</td>
</tr>
<tr>
<td>Kumar, 2010 91</td>
<td>PC</td>
<td>789</td>
<td>USA</td>
<td>Children enrolled as part an ongoing family-based food allergy study in Chicago, IL</td>
<td>Egg, peanut, tree nut, shellfish, fish, sesame, rice, wheat, cow's milk</td>
<td>Interview and questionnaire 5</td>
<td></td>
<td>FA (history of reaction to food plus sensitisation to food)</td>
</tr>
<tr>
<td>Kurukulaarat chy, 2004 92; Tariq, 1998 93</td>
<td>PC</td>
<td>1218</td>
<td>UK</td>
<td>Isle of Wight Prevention Study: Population based birth cohort of mainly Caucasian infants born in the Isle of Wight 1989 and 1990</td>
<td>Cow’s milk</td>
<td>Questionnaire and diary 10, 4</td>
<td></td>
<td>Allergic rhinitis, Eczema (physician assessment); Wheeze (parent report of symptoms); FA (history of reaction to food)</td>
</tr>
<tr>
<td>Kvenshagen, 2011 94; Per Nafstad, 2003 95</td>
<td>PC</td>
<td>2271</td>
<td>Norway</td>
<td>The Environment and Childhood Asthma study in Oslo: Population based birth cohort of newborn children included born in Oslo, Norway in 1992</td>
<td>Fish</td>
<td>Questionnaire 2, 4</td>
<td></td>
<td>Allergic rhinitis (questionnaire with parent report); Eczema (DD); Wheeze (Q or DD of asthma)</td>
</tr>
</tbody>
</table>
### eTable 4. Characteristics of studies examining timing of food introduction and risk of allergic diseases (69 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
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<th>Population</th>
<th>Exposure(s)</th>
<th>Measure</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laubereau, 2003 97</td>
<td>PC</td>
<td>1500</td>
<td>Germany</td>
<td>GINI: Term newborn infants born between September 1995 and July 1998 were recruited from 2 regions of Germany to participate into an intervention program according to risk of allergy</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>3</td>
<td>Eczema (DD)</td>
</tr>
<tr>
<td>Lucas, 1999 98</td>
<td>PC</td>
<td>447</td>
<td>UK</td>
<td>Participants in a RCT of a formula intervention and screened candidates ineligible for randomisation</td>
<td>Cow’s milk</td>
<td>Interview and questionnaire</td>
<td>0.75</td>
<td>Eczema (parent reported); Wheeze (DD)</td>
</tr>
<tr>
<td>Luccioli, 2014 99</td>
<td>PC</td>
<td>1542</td>
<td>USA</td>
<td>Sample of the study population of The Infant Feeding Practices Study II (IFPS II), a panel survey, representative of pregnant women in USA in 2005, and who were present in the year 6 of follow-up</td>
<td>Wheat, cow’s milk, egg, fish, peanut, soy</td>
<td>Questionnaire</td>
<td>6</td>
<td>FA (mother was asked about physician diagnosis of food allergy)</td>
</tr>
<tr>
<td>Midwinter, 1987 100</td>
<td>PC</td>
<td>455</td>
<td>UK</td>
<td>Children born to parents with a family history of atopy in 1979-1981</td>
<td>Cow’s milk, soya</td>
<td>Interview and questionnaire</td>
<td>5</td>
<td>Eczema (DD); Wheeze (Q or DD of asthma)</td>
</tr>
<tr>
<td>Mihrshahi, 2007 101</td>
<td>PC</td>
<td>516</td>
<td>Australia</td>
<td>CAPS: Pregnant women from antenatal clinics of 6 hospitals of Sydney between 1997 and 1999 with unborn children at high risk of asthma</td>
<td>Cow’s milk, eggs, nuts or fish</td>
<td>Interview</td>
<td>5</td>
<td>Eczema, Wheeze (parent reported plus DD); AS (SPT-any)</td>
</tr>
<tr>
<td>Morgan, 2004 102</td>
<td>PC</td>
<td>257</td>
<td>UK</td>
<td>Healthy preterm birth (&lt;37 weeks gestational) were recruited from a cross section of socioeconomic groups in southeast England using the Royal Surrey County Hospital (Guildford), St Peter’s Hospital (Chertsey), and Frimley Park Hospital (Frimley)</td>
<td>Cereal, cow’s milk, fish, egg</td>
<td>Interview</td>
<td>1</td>
<td>Eczema (physician assessment and parent reported)</td>
</tr>
<tr>
<td>Niinivirta, 2014 103</td>
<td>PC</td>
<td>256</td>
<td>Finland</td>
<td>Mother over 18, pregnancy &lt;17 weeks and the child having increased risk for allergy</td>
<td>Cow’s milk, egg, fish, cereal</td>
<td>Diary</td>
<td>4</td>
<td>Eczema (physician assessment)</td>
</tr>
</tbody>
</table>
## eTable 4. Characteristics of studies examining timing of food introduction and risk of allergic diseases (69 observational studies)

<table>
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<tr>
<th>Study</th>
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<th>Measure</th>
<th>Age (yrs)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Nwaru, 2013a</td>
<td>PC</td>
<td>1924</td>
<td>UK</td>
<td>(SEATON) Study of Eczema and Asthma To Observe the influence of Nutrition: recruited healthy pregnant women attending an antenatal clinic</td>
<td>Cereal, cow’s milk, egg, fish</td>
<td>Diary</td>
<td>10</td>
<td>Eczema, Wheeze (ISAAC Q)</td>
</tr>
<tr>
<td>Nwaru, 2013b, Virtanen 2010, Nwaru, 2010, Nwaru, 2013</td>
<td>PC</td>
<td>6071</td>
<td>Finland</td>
<td>DIPP: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland</td>
<td>Cow’s milk, wheat, oats, rye, egg, fish, wheat</td>
<td>Interview and questionnaire</td>
<td>0, 5</td>
<td>Allergic rhinitis (parent report ISAAC Q); Eczema, Wheeze (DD ISAAC Q); AS (sIgE aero, sIgE cow’s milk, sIgE egg, sIgE food, sIgE-any)</td>
</tr>
<tr>
<td>Oddy, 1999, Oddy, 2000, Oddy 2004</td>
<td>PC</td>
<td>1977</td>
<td>Australia</td>
<td>Western Australian Pregnancy Cohort: Population based cohort of infants from public antenatal clinic in Perth Western between 1989 and 1992</td>
<td>Cow’s milk</td>
<td>Diary and questionnaire</td>
<td>6</td>
<td>Wheeze (parent reported); AS (SPT aero)</td>
</tr>
<tr>
<td>Ostergaard, 1985</td>
<td>PC</td>
<td>25</td>
<td>Denmark</td>
<td>Full term infants born at the Department of Obstetrics, Aalborg Hospital North, Denmark, from 1979 to 1980 with no family history of atopic disease (eczema, asthma, rhinitis, urticaria)</td>
<td>Cow’s milk</td>
<td>Interview and questionnaire</td>
<td>0.5</td>
<td>AS (Total IgE)</td>
</tr>
<tr>
<td>Peters, 1987</td>
<td>PC</td>
<td>1192</td>
<td>UK</td>
<td>British Cohort Study (bsc70): sample of all infants born in 1970 in Britain</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>5</td>
<td>Eczema (parent reported)</td>
</tr>
<tr>
<td>Poysa, 1990</td>
<td>PC</td>
<td>91</td>
<td>Finland</td>
<td>High risk infant born between 1979 and 1980</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>0, 1</td>
<td>AS (total IgE)</td>
</tr>
<tr>
<td>Poole, 2006</td>
<td>PC</td>
<td>1612</td>
<td>UK</td>
<td>DAISY: Prospective birth cohort of children at increased risk for TIDM recruited from 1993 to 2004 in Denver, Colorado US were screened for human leukocyte antigen (HLA) genotype associated with celiac disease and TIDM</td>
<td>Wheat</td>
<td>Questionnaire</td>
<td>0-4</td>
<td>FA (DD plus positive IgE)</td>
</tr>
</tbody>
</table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Roduit, 2012</td>
<td>PC</td>
<td>1041</td>
<td>Austria, Finland, France, Germany, and Switzerland</td>
<td>PASTURE: Population based birth cohort with women recruited in third trimester of pregnancy from rural areas in 5 European countries (Austria, Finland, France, Germany, and Switzerland) and from families living in a farm and from families not living on a farm of the same area</td>
<td>Cereal, cow’s milk, egg, fish, nuts, soya</td>
<td>Diary</td>
<td>4</td>
<td>Eczema (DD)</td>
</tr>
<tr>
<td>Ruiz, 1992</td>
<td>PC</td>
<td>39</td>
<td>UK</td>
<td>Infants with one allergic parent born between 1987 and 1989</td>
<td>Cow’s milk, egg</td>
<td>Interview and questionnaire</td>
<td>1</td>
<td>Eczema (physician assessment - Hanifin and Rajka criteria)</td>
</tr>
<tr>
<td>Saarinen, 1979</td>
<td>PC</td>
<td>236</td>
<td>Finland</td>
<td>Newborns born at the Helsinki University Central Hospital in the 1st 3 months of 1975, predominantly with upper-middle class parents</td>
<td>Cow’s milk</td>
<td>Diary and interview</td>
<td>1, 3</td>
<td>Eczema (physician assessment); FA (history of allergy - skin reaction or vomiting after ingestion at home)</td>
</tr>
<tr>
<td>Saarinen, 1980</td>
<td>PC</td>
<td>375</td>
<td>Finland</td>
<td>Children born in Helsinki 1978-1979 with and without a history of citrus/fish exclusion during infancy</td>
<td>Fish</td>
<td>Interview</td>
<td>3</td>
<td>FA (OFC)</td>
</tr>
<tr>
<td>Shohet, 1985</td>
<td>PC</td>
<td>368</td>
<td>Israel</td>
<td>Healthy babies at 3-6 months of age without eczema were recruited in 1980</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>0.5</td>
<td>Eczema (physician assessment - Hanifin and Lobitz criteria)</td>
</tr>
<tr>
<td>Sicherer, 2010</td>
<td>PC</td>
<td>503</td>
<td>USA</td>
<td>The Consortium of Food Allergy Research: infants at 3 to 15 months of age with likely egg or milk allergy but without previously known peanut allergy</td>
<td>Soya</td>
<td>Questionnaire</td>
<td>0.8</td>
<td>AS (sIgE peanut)</td>
</tr>
<tr>
<td>Simon, 2008</td>
<td>PC</td>
<td>372</td>
<td>USA</td>
<td>CAS: Middle class mothers enrolled in a health maintenance organisation between 1987 and 1989</td>
<td>Cow’s milk</td>
<td>Interview and records</td>
<td>0-6</td>
<td>Wheeze (parent reported wheeze up to 3 years and physical assessment at 7 years)</td>
</tr>
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<tr>
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<th>Country</th>
<th>Population</th>
<th>Exposure(s)</th>
<th>Measure</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snijders, 2008</td>
<td>PC</td>
<td>2510</td>
<td>Netherlands</td>
<td>KOALA: Population based birth cohort with healthy pregnant women recruited in week 10-14 of their pregnancy from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain and through posters in organic food shops, anthroposophical, physician offices, and midwives.</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>2</td>
<td>Eczema (UK Working Party criteria); Wheeze (parent report of DD); AS (sIgE aero, sIgE any, sIgE cow's milk, sIgE egg, sIgE peanut)</td>
</tr>
<tr>
<td>Strachan, 1996</td>
<td>PC</td>
<td>3935</td>
<td>UK</td>
<td>Sheffield child development study: Each baby born in Sheffield since August 1975 has been included in a screening programme to predict the risk of sudden infant death and other perinatal outcomes</td>
<td>Cow's milk</td>
<td>Interview</td>
<td>16</td>
<td>Allergic rhinitis (DD)</td>
</tr>
<tr>
<td>Strassburger, 2010</td>
<td>PC</td>
<td>293</td>
<td>Brazil</td>
<td>Birth cohort study nested in a dietary intervention randomized field trial in the city of São Leopoldo, southern Brazil in 2002</td>
<td>Cow’s milk</td>
<td>Records</td>
<td>3.5</td>
<td>Wheeze (parent report (ISAAC Q)); AS (SPT aero)</td>
</tr>
<tr>
<td>Van Asperen, 1983</td>
<td>PC</td>
<td>79</td>
<td>Australia</td>
<td>Infants with family history of atopy born at two major obstetric units over an 8-month period from 1980 to 1981</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>1.3</td>
<td>Allergic rhinitis, Eczema, Wheeze (physician assessment)</td>
</tr>
<tr>
<td>Wickens, 2011</td>
<td>PC</td>
<td>512</td>
<td>New Zealand</td>
<td>Cohort part of a RCT of daily probiotic supplementation in infants at high risk of allergy</td>
<td>Wheat, nuts,</td>
<td>Unclear</td>
<td>2</td>
<td>AS (SPT aero, SPT food)</td>
</tr>
<tr>
<td>Wright, 1994</td>
<td>PC</td>
<td>747</td>
<td>USA</td>
<td>Tucson Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984</td>
<td>Cow's milk</td>
<td>Questionnaire</td>
<td>0-6</td>
<td>Allergic rhinitis (parent report)</td>
</tr>
<tr>
<td>Zutavern, 2006, Zutavern, 2008</td>
<td>PC</td>
<td>2549</td>
<td>Germany</td>
<td>LISA: Population based cohort study of newborns recruited between 1997 and 1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef</td>
<td>Cereal, egg, fish</td>
<td>Questionnaire</td>
<td>2</td>
<td>Eczema (DD); AS (sIgE any, sIgE food)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Country</td>
<td>Population</td>
<td>Exposure(s)</td>
<td>Measure</td>
<td>aAge (yrs)</td>
<td>Outcomes reported</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
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<td>-----------</td>
<td>------------------</td>
</tr>
<tr>
<td>Burr, 1989</td>
<td>PC</td>
<td>482</td>
<td>UK</td>
<td>Infant recruited through two antenatal clinics in South Wales born to mothers with positive allergy history in at least one member of family, whose mothers were asked to participate in allergy preventive program</td>
<td>Cow’s milk, egg</td>
<td>Diary</td>
<td>1</td>
<td>Eczema (physician assessment); Wheeze (parent report)</td>
</tr>
<tr>
<td>Moore, 1985</td>
<td>PC</td>
<td>475</td>
<td>UK</td>
<td>Infants born in a hospital in 1979-1980 with family history of eczema or asthma (high risk of disease)</td>
<td>Cow’s milk, soya</td>
<td>Diary and interview</td>
<td>1</td>
<td>Eczema (physician assessment)</td>
</tr>
<tr>
<td>Porch, 1998</td>
<td>PC</td>
<td>130</td>
<td>USA</td>
<td>infants recruited from prenatal services in New Orleans US with family history of allergy</td>
<td>Soya</td>
<td>Interview</td>
<td>1</td>
<td>Eczema (physician assessment)</td>
</tr>
<tr>
<td>Marini, 1996</td>
<td>PC</td>
<td>68</td>
<td>Italy</td>
<td>Infants with family history of allergy born in maternity wards of 3 hospitals from 1989 whose mothers were refused to participate in an allergy prevention intervention program</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>1</td>
<td>Allergic rhinitis, Eczema, wheeze (physician assessment plus parent reported)</td>
</tr>
<tr>
<td>Ivakhnenko, 2013</td>
<td>RC</td>
<td>1000</td>
<td>Ukraine</td>
<td>One year follow up survey of a survey of full-term infants 1-18 months from families resident in Kyiv</td>
<td>Cow’s milk</td>
<td>Interview and questionnaire</td>
<td>1, 2</td>
<td>FA (I or Q)</td>
</tr>
<tr>
<td>Maskell, 2011; Grimshaw, 2013; Grimshaw 2015</td>
<td>NCC</td>
<td>823</td>
<td>UK</td>
<td>EuroPrevall (UK birth cohort): cases were infants with food allergy, each matched to two controls</td>
<td>Wheat, cow’s milk, egg, fish, tree nuts, peanuts</td>
<td>Diary and interview</td>
<td>1, 2</td>
<td>FA (DD with DBPCFC)</td>
</tr>
<tr>
<td>Sariachvili, 2010</td>
<td>NCC</td>
<td>557</td>
<td>Belgium</td>
<td>PIPCO Cohort: cases and controls with data regarding development of eczema and timing of introduction of solid foods were identified from this prospective cohort: Belgium.</td>
<td>Cow’s milk, cereal, egg, fish</td>
<td>Questionnaire</td>
<td>4</td>
<td>Eczema (parent reported (ISAAC Q))</td>
</tr>
</tbody>
</table>
### eTable 4. Characteristics of studies examining timing of food introduction and risk of allergic diseases (69 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Country</th>
<th>Population</th>
<th>Exposure(s)</th>
<th>Measure</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Shoshan M, 2015</td>
<td>CC</td>
<td>480/4950</td>
<td>Canada</td>
<td>SPAACE random telephone survey: cases were self-reported probable food allergy; controls were age-matched respondents with no self-reported food allergy</td>
<td>Cow’s milk, soya, egg, fish, peanut, tree nuts, sesame, shellfish</td>
<td>Interview</td>
<td>All ages</td>
<td>FA (focussed telephone questionnaire – self-reported clinical history consistent with IgE-mediated food allergy or physician diagnosis of food allergy)</td>
</tr>
<tr>
<td>DesRoches, 2010</td>
<td>CC</td>
<td>403</td>
<td>Canada</td>
<td>Cases and controls were recruited from the Paediatric University Centre between 1998-2004</td>
<td>Egg, peanut and other nuts, soya, cow’s milk</td>
<td>Questionnaire</td>
<td>&lt;1.5</td>
<td>FA (history of a clinical reaction within 60 minutes of exposure to peanuts, combined with positive IgE or SPT to peanut)</td>
</tr>
<tr>
<td>Ghaderi, 2014</td>
<td>CC</td>
<td>200</td>
<td>Iran</td>
<td>Sources of cases and controls not specified</td>
<td>Cow’s milk</td>
<td>Questionnaire and interview</td>
<td>5</td>
<td>Eczema (DD)</td>
</tr>
<tr>
<td>Ibsaine, 2014</td>
<td>CC</td>
<td>450</td>
<td>Algeria</td>
<td>Cases diagnosed over a period of 6 years (2004-2010) and 300 controls matched for sex - prospective case-control study</td>
<td>Cow’s milk</td>
<td>Unclear</td>
<td>1</td>
<td>FA (unclear)</td>
</tr>
<tr>
<td>Lopez Campos, 2001</td>
<td>CC</td>
<td>75</td>
<td>Mexico</td>
<td>Asthmatic patients recruited from allergy clinics and control patients from familial medicine clinics of Hospital de Especialidades, Mexico.</td>
<td>Egg</td>
<td>Questionnaire</td>
<td>6, 10</td>
<td>Wheeze (DD asthma)</td>
</tr>
<tr>
<td>Wickens, 2001</td>
<td>CC</td>
<td>474</td>
<td>New Zealand</td>
<td>Cases and potential controls selected from the ISAAC Wellington survey participants aged 7-9 years</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>6.5</td>
<td>Wheeze (parent reported and DD asthma (ISAAC))</td>
</tr>
<tr>
<td>Alper, 2006</td>
<td>CS</td>
<td>857</td>
<td>Turkey</td>
<td>7-year-old children randomly selected from seven primary schools</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>7</td>
<td>Wheeze (parent reported)</td>
</tr>
<tr>
<td>Kucukosmanoglu, 2008</td>
<td>CS</td>
<td>1015</td>
<td>Turkey</td>
<td>Participants were all born in Okmeydani Teaching Hospital, Turkey, between 2001-2, with and without allergic sensitisation.</td>
<td>Egg</td>
<td>Interview</td>
<td>1</td>
<td>AS (SPT-egg)</td>
</tr>
<tr>
<td>Miyake, 2003</td>
<td>CS</td>
<td>5614</td>
<td>Japan</td>
<td>Participants were 12-15 years olds from public schools in Suita, Japan.</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>15</td>
<td>Allergic rhinitis, Eczema, Wheeze (parent reported (ISAAC Q))</td>
</tr>
<tr>
<td>Salem, 2002</td>
<td>CS</td>
<td>424</td>
<td>Iraq</td>
<td>All children 0.16-2 years old, living in three areas of Basra, Iraq, were included in the study.</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>0.16, 5</td>
<td>Wheeze (parent report)</td>
</tr>
</tbody>
</table>
### eTable 4. Characteristics of studies examining timing of food introduction and risk of allergic diseases (69 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Country</th>
<th>Population</th>
<th>Exposure(s)</th>
<th>Measure</th>
<th>aAge (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suwanpromma, 2012</td>
<td>CS</td>
<td>215</td>
<td>Thailand</td>
<td>Participants randomly recruited school children aged 6-18 years from Bangkok</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>6, 18</td>
<td>Lung function (Spirometry: FEV₁:FVC ratio &lt;0.8 considered to demonstrate airflow obstruction)</td>
</tr>
<tr>
<td>Takemura, 2001</td>
<td>CS</td>
<td>2382</td>
<td>Japan</td>
<td>Students from public elementary schools in Tokorozawa</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>6, 15</td>
<td>Wheeze (parent report and DD asthma)</td>
</tr>
</tbody>
</table>

PC prospective cohort; CC case-control study; NCC nested case-control study; CS cross-sectional study; AS allergic sensitisation; FA food allergy; DD doctor diagnosis; BF breastfeeding; eBF exclusive breastfeeding; pHF partially hydrolysed formula; ISAAC International Study of Asthma and Allergies in Children; ECRHS European Community Respiratory Health Survey; BHR bronchial hyper responsiveness; FEV₁ forced expiratory volume in 1 second; FVC forced vital capacity; PC 20% provocative concentration of methacholine resulting in 20% fall in FEV₁; SPT skin prick test; CM cow’s milk; sIgE specific IgE; SCORAD scoring atopic dermatitis; ICS inhaled corticosteroids. Multiple references for a single study refer to multiple publications from the same cohort. aAge at outcome – for some studies outcome data used in the systematic review were derived from evaluations at multiple ages.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. in Intervention Group</th>
<th>No. in Control Group</th>
<th>Intervention characteristics</th>
<th>Population</th>
<th>Country</th>
<th>Disease risk</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyerlein, 2014</td>
<td>RCT</td>
<td>77</td>
<td>73</td>
<td>Introduction of gluten into diet at 6 months, versus delay to 12 months</td>
<td>BABYDIET Study. Infants &lt; 2 months with at least one first-degree relative with type 1 diabetes, no gluten in diet yet, and one of five specific type 1 diabetes-associated HLA genotypes</td>
<td>Germany</td>
<td>High</td>
<td>8</td>
<td>CD (tTG antibody positive in ≥2 samples) TIDM (American Diabetes Association Expert Committee criteria)</td>
</tr>
<tr>
<td>Lionetti, 2014</td>
<td>RCT</td>
<td>416</td>
<td>416</td>
<td>Introduction of food containing gluten (pasta, semolina, and biscuits) at 6 months, versus delay to 12 months</td>
<td>SIGENP Study. Newborns with at least one first-degree relative with celiac disease</td>
<td>Italy</td>
<td>High</td>
<td>7.9</td>
<td>CD (autoimmunity and Marsh 2 or 3 at small-bowel biopsy)</td>
</tr>
<tr>
<td>Sellitto, 2012</td>
<td>RCT</td>
<td>17</td>
<td>13</td>
<td>Daily purified wheat gluten versus daily corn starch from 6 months to 12 months age, at 3-5g daily</td>
<td>Infants of first-degree relatives with biopsy proven CD, and positive for HLA DQ2 or HLA DQ8 genotypes, eBF to 6 months</td>
<td>USA</td>
<td>High</td>
<td>1</td>
<td>CD (tTG ≥ 7 AU and subsequent positive endomysial IgA antibodies)</td>
</tr>
<tr>
<td>Vriezinga, 2014</td>
<td>RCT</td>
<td>483</td>
<td>480</td>
<td>200 mg wheat gluten with 1.8 g of lactose (equivalent to 100 mg of immunologically active gluten) versus 2g lactose daily from 16-24 weeks age</td>
<td>PreventCD Study: Infants aged 0-3 months with ≥first degree relative with biopsy-proven CD, and HLA-DQ2, HLA-DQ8 or DQB1*02 genotype</td>
<td>Croatia, Germany, Hungary, Israel, Italy, the Netherlands, Poland and Spain</td>
<td>High</td>
<td>4</td>
<td>CD (Serological diagnosis: tTG IgA or IgG antibodies; or biopsy as per 1990 ESPGHAN criteria)</td>
</tr>
</tbody>
</table>
eTable 5. Characteristics of studies examining timing of food introduction and autoimmune diseases (5 intervention studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. in Intervention Group</th>
<th>No. in Control Group</th>
<th>Intervention characteristics</th>
<th>Population</th>
<th>Country</th>
<th>Disease risk</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savilahti, 2009&lt;sup&gt;†&lt;/sup&gt;</td>
<td>qRCT</td>
<td>1789</td>
<td>1859</td>
<td>CM formula versus pasteurised human milk from birth for mean 4 days</td>
<td>Term infants in Helsinki fed formula milk before hospital discharge.</td>
<td>Finland</td>
<td>normal</td>
<td>11.5</td>
<td>TIDM (Clinical diagnosis)</td>
</tr>
</tbody>
</table>

RCT randomised controlled trial; qRCT quasi randomised controlled trial; CD coeliac disease; DD doctor diagnosis; CM cow’s milk; eBF exclusive breastfeeding; IgA immunoglobulin A; tTG tissue Transglutaminase; IgA immunoglobulin A; IgG immunoglobulin G; T1DM type 1 diabetes mellitus; ESPGHAN European Society for Paediatric, Gastroenterology, Hepatology and Nutrition; HLA DQ2 or DQ8 cell surface receptor protein serotype 2 (DQ2) or 8 (DQ8). Multiple references for a single study refer to multiple publications from the same trial. *Disease risk is high where the population studied were at high inherited risk of autoimmune disease. **Age at outcome – for some studies outcome data used in the systematic review were derived from evaluations at multiple ages.
**eTable 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Exposure</th>
<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chmiel, 2015</td>
<td>PC</td>
<td>2291</td>
<td>Cereal</td>
<td>Questionnaire and interview</td>
<td>BABYDIAB 1989-2000 and BABYDIET 2000-2006 Population from 2 prospective cohort, offspring or siblings of patients with T1DM</td>
<td>Germany</td>
<td>25</td>
<td>T1DM (Islet autoimmunity: IAA, GADA and IA2A); CD (Antibodies to tTG-C)</td>
</tr>
<tr>
<td>Couper, 1999; Couper, 2009</td>
<td>PC</td>
<td>548</td>
<td>Cow's milk, cereal</td>
<td>Diary and questionnaire</td>
<td>Australian BABYDIAB: Birth cohort of newborns with a first-degree relative with type 1 diabetes were recruited during the pregnancy in Victoria and South Australia, Australia in 1993</td>
<td>Australia</td>
<td>2.4, 1.7</td>
<td>T1DM (Islet autoimmunity: IAA, GADA and IA2A)</td>
</tr>
<tr>
<td>Holmberg, Karlen, Wahlberg, Wahlberg, Welander,</td>
<td>PC</td>
<td>8715</td>
<td>Cow's milk, cereal</td>
<td>Questionnaire</td>
<td>ABIS: Population based birth cohort of children born in Southeast Sweden between 1997 and 1999</td>
<td>Sweden</td>
<td>1, 2, 5.5</td>
<td>T1DM (Islet autoimmunity: GADA, IAA, and/or IA2A); CD (DD plus IgA-tTG plus symptoms)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Generation R study: Population based cohort study. This analysis involved those at risk of CD based on HLA type.</td>
<td>Netherlands</td>
<td>6</td>
<td>CD (tTG antibody positive)</td>
</tr>
<tr>
<td>Jansen, 2014</td>
<td>PC</td>
<td>8305</td>
<td>Cereal</td>
<td>Questionnaire</td>
<td>Children with one or more family members with atopy</td>
<td>Sweden</td>
<td>0.5, 5</td>
<td>T1DM (Islet autoimmunity: GADA, IAA, IA2A)</td>
</tr>
<tr>
<td>Ludvigsson, 2003</td>
<td>PC</td>
<td>186</td>
<td>Cow's milk, cereal</td>
<td>Questionnaire</td>
<td>Childhood Diabetes in Finland Study: Unaffected siblings of index children newly diagnosed with T1DM aged between 3 and 19 years old</td>
<td>Finland</td>
<td>&lt;25</td>
<td>T1DM (Islet autoimmunity: ICA, IAA, GADA, IA2A); CD (DD plus IgA-tTG plus symptom)</td>
</tr>
<tr>
<td>Virtanen, 1998</td>
<td>PC</td>
<td>697</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td></td>
<td>Finland</td>
<td>&lt;25</td>
<td></td>
</tr>
</tbody>
</table>
### eTable 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Exposure</th>
<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hummel, 2007</td>
<td>PC</td>
<td>1282</td>
<td>Cow's milk, cereal</td>
<td>Questionnaire</td>
<td>German BABYDIAB: Birth cohort of newborns with a first-degree relative with type 1 diabetes were recruited during the pregnancy in Germany between 1989 and 2000</td>
<td>Germany</td>
<td>4, 5</td>
<td>T1DM (Islet autoimmunity: IAA, GADA or IA2); CD (IgA-tTG)</td>
</tr>
<tr>
<td>Ziegler, 2003</td>
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<tr>
<td>Aronson, 2016</td>
<td>NCC</td>
<td>146/4 36</td>
<td>Gluten containing cereals, wheat</td>
<td>Questionnaire</td>
<td>TEDDY (Determinants of Diabetes in the Young): Children were recruited between 2004 and 2010. Cases were defined as children with biopsy-confirmed CD</td>
<td>Sweden</td>
<td>3.2 (38 months)</td>
<td>CD (cases were defined as children with +tTG plus biopsy-confirmed CD)</td>
</tr>
<tr>
<td>Frederiksen, 2012 and 2013</td>
<td>PC, NCC</td>
<td>1886</td>
<td>Cereal, cow's milk, egg</td>
<td>Interview and questionnaire</td>
<td>DAISY: Prospective birth cohort of children at increased risk for T1DM (relative with T1DM via registries and hospital records) recruited from 1993 to 2004 in Denver, Colorado US were screened for human leukocyte antigen (HLA) genotype associated with celiac disease and T1DM</td>
<td>USA</td>
<td>4, 7, 9</td>
<td>T1DM (DD; Islet autoimmunity: GADA or IA2A or IAA) CD (Positive IgA-tTG)</td>
</tr>
<tr>
<td>Vaarala, 1999</td>
<td>PC, NCC</td>
<td>5619</td>
<td>Cereal, cow's milk, egg</td>
<td>Interview and questionnaire</td>
<td>DIPP: Prospective birth cohort of children at high risk of T1DM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland</td>
<td>Finland</td>
<td>&lt;2, &lt;10, &lt;4, &lt;19</td>
<td>T1DM (Isle autoimmunity: GADA or IAA or IA2A)</td>
</tr>
<tr>
<td>Virtanen, 2006 and 2011</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Kimpimaki, 2001</td>
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<td></td>
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<tr>
<td>Lempainen, 2012</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savilahti, 2009</td>
<td>NCC</td>
<td>6209</td>
<td>Cow's milk, cereal</td>
<td>Records and diary</td>
<td>Cases and controls taken from the NHI database, Finland</td>
<td>Finland</td>
<td>11.5</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Ascher, 1997</td>
<td>CC</td>
<td>81</td>
<td>Cow's milk, cereal</td>
<td>Interview</td>
<td>Cases were diagnosed with CD between 1970 and 1991 at the East University Hospital, Göteborg: controls were older siblings of cases without CD.</td>
<td>Sweden</td>
<td>&lt;18</td>
<td>CD (biopsy, ESPGHAN criteria)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Exposure</th>
<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>^aAge (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alves, 2012</td>
<td>CC</td>
<td>246</td>
<td>Cow’s milk, cereal</td>
<td>Interview</td>
<td>Cases with T1DM were sourced from hospital paediatric endocrinology clinics after diagnosis and controls were unaffected siblings</td>
<td>Brazil</td>
<td>6.7, 9</td>
<td>T1DM (DD; WHO criteria)</td>
</tr>
<tr>
<td>Auricchio, 1983</td>
<td>CC</td>
<td>1104</td>
<td>Cereal</td>
<td>Interview and records</td>
<td>Cases were children with CD and controls were their unaffected siblings</td>
<td>Italy</td>
<td>&lt;18</td>
<td>CD (biopsy, ESPGHAN criteria)</td>
</tr>
<tr>
<td>Baruah, 2011</td>
<td>CC</td>
<td>86</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>Cases were T1DM treated on an endocrinology ward &amp; matched controls were recruited from other wards or among family members of medical professionals</td>
<td>India</td>
<td>&lt;18</td>
<td>T1DM (DD; history of diabetic keto acidosis or documentation of spontaneous ketonuria)</td>
</tr>
<tr>
<td>Baron, 2005</td>
<td>CC</td>
<td>444</td>
<td>Cereal</td>
<td>Interview</td>
<td>Cases were identified from the EPIMAD registry with matched controls from the same area identified by random digit dialling</td>
<td>France</td>
<td>&lt;17</td>
<td>Crohn’s disease, Ulcerative colitis (all DD)</td>
</tr>
<tr>
<td>Bodington, 1994</td>
<td>CC</td>
<td>393</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>UK study of T1DM cases diagnosed 1980-90 and matched controls from a Population Register in Leicestershire.</td>
<td>UK</td>
<td>&lt;15</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Ellis, 2012</td>
<td>CC</td>
<td>655</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>CLARITY: cases were recruited during a clinic visit to Royal Children's Hospital, with diagnosed JIA using ILAR criteria: controls were patients in for elective surgery</td>
<td>Australia</td>
<td>18</td>
<td>JIA (DD, ILAR criteria)</td>
</tr>
<tr>
<td>Esfajani, 2001</td>
<td>CC</td>
<td>104</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Case children selected from an endocrine clinic in Tehran, with controls selected from a paediatric outpatient department</td>
<td>Iran</td>
<td>&lt;14</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>EURODIAB, 2002</td>
<td>CC</td>
<td>2226</td>
<td>Cow’s milk</td>
<td>Interview and questionnaire</td>
<td>EURODIAB (Austria, Latvia, Lithuania, Luxembourg &amp; UK): Cases with T1DM were selected from a population-based register and controls from population registers, schools &amp; polyclinics</td>
<td>Austria, Latvia, Lithuania, Luxembour</td>
<td>&lt;15</td>
<td>T1DM (DD)</td>
</tr>
</tbody>
</table>
### Table 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Exposure</th>
<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>^Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faith-Magnusson, 1996</td>
<td>CC</td>
<td>336</td>
<td>Cereal</td>
<td>Questionnaire</td>
<td>Cases were children with CD registered in 3 paediatric departments in Ostergotland County, Sweden, with positive biopsy under the age of 2 years at biopsy. Controls were matched children from same county.</td>
<td>Sweden</td>
<td>&lt;2</td>
<td>CD (biopsy, ESPGHAN criteria)</td>
</tr>
<tr>
<td>Gimeno, 1997</td>
<td>CC</td>
<td>626</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases with T1DM were identified through a social education program for young diabetics or through the Hospital Sao Paulo. Controls were matched non-diabetic children.</td>
<td>Brazil</td>
<td>&lt;18</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Greco, 1988</td>
<td>CC</td>
<td>2150</td>
<td>Cereal</td>
<td>Questionnaire</td>
<td>Cases were celiac children who completed the ESPGAN diagnostic protocol from 1979-83 and controls were healthy children from same region born in same years as the patients.</td>
<td>Italy</td>
<td>2, 15</td>
<td>CD (biopsy, ESPGHAN criteria)</td>
</tr>
<tr>
<td>Hypponen, 1999; Virtanen, 1992; Virtanen, 1993</td>
<td>CC</td>
<td>1380</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Finnish children &lt;14 years diagnosed between 1986-1989, with matched controls selected from the Finnish Population Registry.</td>
<td>Finland</td>
<td>8.2, 7-14</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Ivarsson, 2002</td>
<td>CC</td>
<td>254/ 1018</td>
<td>Cereal</td>
<td>Questionnaire</td>
<td>Cases were selected from the CD Register and were matched to 2 controls recruited from the National Population Register: Sweden.</td>
<td>Sweden</td>
<td>2, 17</td>
<td>CD (small intestine biopsies)</td>
</tr>
<tr>
<td>Kostraba, 1992</td>
<td>CC</td>
<td>372</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases were selected from hospital IDDM registers and controls were the non-diabetic siblings of subjects: Pittsburgh, USA. All black population.</td>
<td>Pittsburg, USA</td>
<td>8.6, 10.1</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Kostraba, 1993</td>
<td>CC</td>
<td>306</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases were found through the IDDM Registry &amp; controls recruited from licensed motor vehicle register, both in Colorado, USA.</td>
<td>Colorado, USA</td>
<td>&lt;18</td>
<td>T1DM (DD)</td>
</tr>
</tbody>
</table>
### eTable 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)

<table>
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<tr>
<th>Study</th>
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<th>Country</th>
<th>^aAge (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcova, 2006</td>
<td>CC</td>
<td>2334</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases were identified from the Czech Childhood Diabetes Register, with unrelated aged-match controls selected from among the schoolmates of cases</td>
<td>Czech Republic</td>
<td>&lt;15</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Marshall, 2004</td>
<td>CC</td>
<td>577</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>Cases were T1 diabetics registered at a Paediatric Diabetes Clinic, Lancashire, UK, 1998. Controls were children, without chronic disease, selected from the local Health Authority Register</td>
<td>UK</td>
<td>&lt;16</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Meloni, 1997</td>
<td>CC</td>
<td>200</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases were diabetic children followed up by the Paediatric Department of the University of Sassari, Sardinia, with controls selected from children also admitted to the same hospital but with no personal or family history of T1DM</td>
<td>Sardinia</td>
<td>&lt;17</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Myleus, 2012</td>
<td>CC</td>
<td>954</td>
<td>Cereal</td>
<td>Questionnaire</td>
<td>Cases were included from the Swedish National Childhood Celiac Disease Register with matched controls selected randomly from the National Population Register</td>
<td>Sweden</td>
<td>&lt;2</td>
<td>CD (biopsy, ESPGHAN criteria)</td>
</tr>
<tr>
<td>Pacilio, 2010</td>
<td>CC</td>
<td>278</td>
<td>Cereal</td>
<td>Unknown</td>
<td>Cases were children 0.5-2 years old with age matched healthy controls</td>
<td>Not known</td>
<td>2</td>
<td>CD (unclear)</td>
</tr>
<tr>
<td>Perez-Bravo, 1996,</td>
<td>CC</td>
<td>250</td>
<td>Cow’s milk</td>
<td>Interview and questionnaire</td>
<td>Cases were T1DMs selected from the Santiago de Chile registry and controls were randomly recruited from several schools</td>
<td>Chile</td>
<td>&lt;15, 8</td>
<td>T1DM (DD), WHO criteria</td>
</tr>
</tbody>
</table>
### eTable 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)

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<tr>
<th>Study</th>
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<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>^a Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters, 2001^19</td>
<td>CC</td>
<td>270</td>
<td>Cereal</td>
<td>Questionnaire</td>
<td>Cases were diagnosed with CD aged &lt;10y between 1995-96 and controls recruited from a matched random group identified through the population registry of the two federal states (Hamburg and Schleswig)</td>
<td>Germany</td>
<td>&lt; 10</td>
<td>CD (biopsy, ESPGHAN criteria)</td>
</tr>
<tr>
<td>Roman, 2010</td>
<td>CC</td>
<td>1488</td>
<td>Gluten</td>
<td>Unknown</td>
<td>REPAC (Prospective observational study and nationwide registry in Spain) including all new CD cases in children (&lt;15 years), from 06–2006 until the 05–2007. Participating centres have a well-established health area and population. Presentation patterns at diagnosis were recorded. Case:control 1:1 study with children paired for age and sex.</td>
<td>Spain</td>
<td>15</td>
<td>CD (DD)</td>
</tr>
<tr>
<td>Rosenbauer, 2007, Rosenbauer, 2008</td>
<td>CC</td>
<td>2631</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>EURODIAB: Cases are newly diagnosed diabetics registered by nationwide active hospital-based surveillance system ESPED and controls from acquaintances of cases.</td>
<td>Germany</td>
<td>&lt;5</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Rosenberg, 1996</td>
<td>CC</td>
<td>419</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases were recruited from the Pediatric Rheumatic Disease Clinic, University of Saskatchewan, and matched controls were identified by the parents of cases.</td>
<td>Canada</td>
<td>&lt;18</td>
<td>JRA (DD; American College of Rheumatology criteria)</td>
</tr>
<tr>
<td>Sadauskaite-Kuehne, 2004, Skrodmeniene, 2010</td>
<td>CC</td>
<td>517</td>
<td>Cow’s milk, eggs</td>
<td>Questionnaire</td>
<td>DEBS Study: cases were newly diagnosed between 1995-2000 in South East Sweden and aged &lt;15</td>
<td>Sweden, Lithuania</td>
<td>7</td>
<td>T1DM (DD)</td>
</tr>
</tbody>
</table>
**eTable 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
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<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>#Age (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipetic, 2005</td>
<td>CC</td>
<td>315</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>Cases were children hospitalised with new diagnosis of T1DM in Belgrade, with controls selected from a population of children treated for skin disease as outpatients</td>
<td>Serbia</td>
<td>&lt;16</td>
<td>T1DM (DD), WHO criteria</td>
</tr>
<tr>
<td>Soltesz, 1994</td>
<td>CC</td>
<td>305</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Hungarian Childhood Diabetes Epidemiology Study Group (part of EUROBIAB/DIAMOND): Cases were newly diagnosed T1DM as per the incidence register for 1990 and matched controls were selected by case families</td>
<td>Hungary</td>
<td>&lt;14</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Strisciuglio, 2016</td>
<td>CC</td>
<td>698</td>
<td>Gluten</td>
<td>Unknown</td>
<td>Cases were children age 1-18 with inflammatory bowel disease; controls were healthy siblings or age- and sex-matched healthy controls.</td>
<td>Italy</td>
<td>&lt;18</td>
<td>Crohn’s disease or ulcerative colitis (unclear)</td>
</tr>
<tr>
<td>Strotmeyer, 2004</td>
<td>CC</td>
<td>690</td>
<td>Cow’s milk, cereal, egg, fish, soya</td>
<td>Questionnaire</td>
<td>WHO Multinational Project for Childhood Diabetes (DiaMond): cases selected from T1DM incidence registries 1985-98 and matched controls from locally resident populations (&gt;95%)</td>
<td>China</td>
<td>9.7</td>
<td>T1DM (DD); WHO criteria</td>
</tr>
<tr>
<td>Svensson, 2005</td>
<td>CC</td>
<td>1186</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases taken from the National Register, diagnosed between 1996-99, and controls from the Population Register</td>
<td>Denmark</td>
<td>8.4</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Telahun, 1994</td>
<td>CC</td>
<td>129</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases selected from attendees of a diabetic clinic and controls from their non-diabetic siblings</td>
<td>Ethiopia</td>
<td>&lt;15</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Thorsdottir, 2000</td>
<td>CC</td>
<td>220</td>
<td>Cow’s milk</td>
<td>Interview</td>
<td>Cases were children with IDDM and controls were children selected by Statistical Bureau of Iceland.</td>
<td>Iceland</td>
<td>12</td>
<td>T1DM (DD)</td>
</tr>
<tr>
<td>Verge, 1994</td>
<td>CC</td>
<td>475</td>
<td>Cow's milk, soya</td>
<td>Questionnaire</td>
<td>Cases taken from an incidence register and controls from school registers in New South Wales</td>
<td>Australia</td>
<td>≤14</td>
<td>T1DM (DD)</td>
</tr>
</tbody>
</table>
**eTable 6. Characteristics of studies examining timing of food introduction and autoimmune diseases (48 observational studies)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
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<th>Measure</th>
<th>Population characteristics</th>
<th>Country</th>
<th>^aAge (yrs)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visalli, 2003</td>
<td>CC</td>
<td>900</td>
<td>Cow's milk, egg, fish</td>
<td>Questionnaire</td>
<td><strong>EURODIAB Italy:</strong> Cases with T1DM selected from within the EURODIAB ACE study, born 1977-89, with controls selected from school records for the same period</td>
<td>Italy</td>
<td>6, 18</td>
<td>T1DM (DD); WHO criteria</td>
</tr>
<tr>
<td>Wadsworth, 1997</td>
<td>CC</td>
<td>639</td>
<td>Cow’s milk</td>
<td>Questionnaire</td>
<td>Cases were newly diagnosed with T1DM &lt;5y in 1992 and controls were selected form District Health Authority Immunisation Register</td>
<td>UK</td>
<td>&lt;5</td>
<td>T1DM (DD)</td>
</tr>
</tbody>
</table>

PC prospective cohort study; NCC nested case-control study; CC case-control study; I Interview; Q questionnaire; R records; DD doctor diagnosis; tTG tissue Transglutaminase; T1DM type 1 diabetes mellitus; IAA insulin autoantibodies; IA2A insulinoma-2-associated autoantibodies; GADA glutamic acid decarboxylase antibodies; ESPGHAN European Society for Paediatric Gastroenterology, Hepatology and Nutrition; ILAR League of Associations for Rheumatology; JRA juvenile rheumatoid arthritis; WHO World Health Organisation. Multiple references for a single study refer to multiple publications from the same cohort. ^aAge at outcome – for some studies outcome data used in the systematic review were derived from evaluations at multiple ages.
### eTable 7. Risk of Bias in studies examining timing of food introduction and allergic diseases (24 intervention trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Assessment</th>
<th>Selection</th>
<th>Attrition</th>
<th>Overall</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellach, 2015 23</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Becker, 2004 24, Chan-Yeung, 2000/5 25, 26, Carlsten 2013 27</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Brown, 1969 28</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>de Jong, 2002 32</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Du Toit, 2016 33,34</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Halmerbauer, 2002 and 2003 35,36</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Hide, 1994 and 1996 37,38</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Johnstone, 1966 43</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Kjellman, 1979 44</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Lowe, 2011 45</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Matthew, 1977 46</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
</tr>
<tr>
<td>Natsume, 2016 47</td>
<td>RCT</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Palmer, 2013 48</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
**eTable 7. Risk of Bias in studies examining timing of food introduction and allergic diseases (24 intervention trials)**

<table>
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<tr>
<th>Study</th>
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<th>Attrition</th>
<th>Overall</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkin, 2016 49</td>
<td>RCT</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Shao, 2006 50</td>
<td>RCT</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Tan, 2016 51</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zeiger, 1989, 1992 and 1994 52 54</td>
<td>RCT</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
</tr>
<tr>
<td>Zhou, 2014 55</td>
<td>RCT</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Gruskay, 1982 56</td>
<td>CCT</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
</tr>
<tr>
<td>Halpern, 1973 57</td>
<td>aCCT</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
</tr>
<tr>
<td>Lindfors, 1988 58 Lindfors, 1992 59</td>
<td>CCT</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
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Risk of Bias was assessed using the Cochrane Collaboration Risk of Bias Tool. Multiple references for a single study refer to multiple publications from the same trial. RCT randomised controlled trial; CCT case–control trial; qRCT quasi randomised controlled trial. aWithin this CCT of infant milk feeding, participants were randomly allocated to early or late introduction of egg yolk. Thus this trial is also an RCT of timing of egg introduction.
**eTable 8. Risk of Bias in studies examining timing of food introduction and allergic diseases (69 observational studies)**

<table>
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<tr>
<th>Study</th>
<th>Design</th>
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### eTable 8. Risk of Bias in studies examining timing of food introduction and allergic diseases (69 observational studies)

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## eTable 8. Risk of Bias in studies examining timing of food introduction and allergic diseases (69 observational studies)

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### eTable 8. Risk of Bias in studies examining timing of food introduction and allergic diseases (69 observational studies)

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Risk of Bias was assessed using the National Institute for Clinical Excellence methodological checklists for cohort and case-control studies. Multiple references for a single study refer to multiple publications from the same cohort. PC prospective cohort; CC case-control study; NCC nested case-control study; CS cross-sectional study.
eTable 9. Risk of Bias in studies examining infant food introduction and autoimmune diseases (5 intervention trials)

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Risk of Bias was assessed using the Cochrane Collaboration Risk of Bias Tool. Multiple references for a single study refer to multiple publications from the same trial. RCT randomised controlled trial; qRCT quasi randomised controlled trial.
**Table 10. Risk of Bias in studies examining infant food introduction and autoimmune diseases (48 observational studies)**

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<tr>
<td>Vaarala, 1999; Virtanen, 2006 and 2011; Kimpimaki, 2001; Lempainen, 2012</td>
<td>PC, NCC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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</tr>
<tr>
<td>Savilahti, 2009</td>
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<td>Study</td>
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<td>Confounding</td>
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<td>Conflict of Interest</td>
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<tr>
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<tr>
<td>Ascher, 1997 181</td>
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<tr>
<td>Alves, 2012 182</td>
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<tr>
<td>Auricchio, 1983 183</td>
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<td>Baruah, 2011 184</td>
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<tr>
<td>Baron, 2005 185</td>
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<tr>
<td>Bodington, 1994 186</td>
<td>CC</td>
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<tr>
<td>Ellis, 2012 187</td>
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<td>Esfarjani, 2001 188</td>
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<tr>
<td>EURODIAB, 2002 189</td>
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<tr>
<td>Rami, 1999 190</td>
<td>CC</td>
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<tr>
<td>Falth-Magnusson, 1996 16</td>
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<td>Unclear</td>
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</tr>
<tr>
<td>Gimeno, 1997 191</td>
<td>CC</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
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<tr>
<td>Greco, 1988 192</td>
<td>CC</td>
<td>Low</td>
<td>Low</td>
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<td>Hypponen, 1999 193; Virtanen, 1992 194; Virtanen, 1993 195</td>
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<tr>
<td>Ivarsson, 2002 17</td>
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<td>High</td>
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### Table 10. Risk of Bias in studies examining infant food introduction and autoimmune diseases (48 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Assessment</th>
<th>Selection</th>
<th>Confounding</th>
<th>Overall</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kostraba, 1992 (196)</td>
<td>CC</td>
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<td>Low</td>
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<td>Low</td>
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<tr>
<td>Kostraba, 1993 (197)</td>
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<tr>
<td>Malcova, 2006 (198)</td>
<td>CC</td>
<td>High</td>
<td>High</td>
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</tr>
<tr>
<td>Marshall, 2004 (199)</td>
<td>CC</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
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<td>Low</td>
</tr>
<tr>
<td>Meloni, 1997 (200)</td>
<td>CC</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Myleus, 2012 (201)</td>
<td>CC</td>
<td>Low</td>
<td>High</td>
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<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Pacilio, 2010 (202)</td>
<td>CC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Perez-Bravo, 1996 (203);</td>
<td>CC</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Pérez-Bravo, 2003 (204)</td>
<td>CC</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Peters, 2001 (19)</td>
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<td>Unclear</td>
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<tr>
<td>Roman, 2010 (205)</td>
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<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
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<tr>
<td>Rosenbauer, 2007 (206);</td>
<td>CC</td>
<td>High</td>
<td>High</td>
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<td>Low</td>
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<tr>
<td>Rosenbauer, 2008 (207)</td>
<td>CC</td>
<td>High</td>
<td>High</td>
<td>Low</td>
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<td>Low</td>
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<tr>
<td>Rosenberg, 1996 (208)</td>
<td>CC</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
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<tr>
<td>Sadauskaite-Kuehne, 2004 (209)</td>
<td>CC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Skrodeniene, 2010 (210)</td>
<td>CC</td>
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<tr>
<td>Sipetic, 2005 (211)</td>
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<td>High</td>
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</table>
### eTable 10. Risk of Bias in studies examining infant food introduction and autoimmune diseases (48 observational studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Assessment</th>
<th>Selection</th>
<th>Confounding</th>
<th>Overall</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soltesz, 1994 212</td>
<td>CC</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Strisciuglio, 2016 213</td>
<td>CC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Strotmeyer, 2004 214</td>
<td>CC</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
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<tr>
<td>Svensson, 2005 215</td>
<td>CC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Telahun 1994 216</td>
<td>CC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Thorsdottir, 2000 217</td>
<td>CC</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Verge, 1994 218</td>
<td>CC</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Visalli, 2003 219</td>
<td>CC</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Wadsworth, 1997 220</td>
<td>CC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Low</td>
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</tbody>
</table>

Risk of Bias was assessed using the National Institute for Clinical Excellence methodological checklists for cohort and case-control studies. Multiple references for a single study refer to multiple publications from the same cohort. PC prospective cohort; CC case-control study; NCC nested case-control study.
### eTable 11. Summary of all review findings

<table>
<thead>
<tr>
<th>Report</th>
<th>Study Design</th>
<th>Setting</th>
<th>Interventions Assessed</th>
<th>Outcome Assessment</th>
<th>Age at Outcome Assessment</th>
<th>N</th>
<th>Risk of Bias</th>
<th>Main Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wheeze Intervention</strong></td>
<td>12 RCT, 1 qRCT, 3 CCT</td>
<td>Europe, 7 North America</td>
<td>15 Cow’s milk, 8 Soya, 5 Egg, 5 Fish, 4 Peanut, 3 Wheat, 2 Tree Nuts, 4 Multifaceted studies</td>
<td>7 Doctor Diagnosis, 5 Parent Reported Symptoms, 4 Parent Report of Doctor Diagnosis, 1 Lung Function</td>
<td>12 studies, ≤ 4 years; 11 studies ≤ 14 years; 2 studies ≥ 15 years</td>
<td>8,433</td>
<td>High in 7 studies (44%) due to selection bias (5), attrition bias (2) and assessment bias (2)</td>
<td>Early cow’s milk and wheeze at ≤4 years RR = 1.12 (0.77 to 1.62)</td>
<td>Analyses dominated by multifaceted studies, and studies comparing cow’s milk with soya formula. One small study at high risk of bias found increased wheeze with cow’s milk compared to soya, but this was not supported by other trials. Data for egg, soy, nuts, fish and wheat were sparse.</td>
</tr>
<tr>
<td><strong>Wheeze Observational</strong></td>
<td>23 PC, 5 CC, 2 CS</td>
<td>Europe, 1 North America, 8 Asia Pacific, 2 Middle East, 2 Latin America</td>
<td>17 Cow’s milk, 3 Soya, 9 Egg, 8 Fish, 1 Nut, 6 Cereal or Gluten, 1 Any allergenic food</td>
<td>15 Doctor Diagnosis, 16 Parent Reported Symptoms, 3 Parent Report of Doctor Diagnosis, 1 Lung Function</td>
<td>20 studies, ≤ 4 years; 19 studies ≤ 14 years; 3 studies ≥ 15 years</td>
<td>65,601</td>
<td>High in 11 studies (37%) due to confounding bias (9) and selection bias (3)</td>
<td>Early fish and recurrent wheeze at ≤4 years OR = 0.72 (0.59 to 0.87)</td>
<td>Five other studies, with 13,033 participants (compared with 11,155 in the meta-analysis) could not be included in meta-analysis of fish introduction, and showed no association with risk of recurrent wheeze at ≤4 years. Data for egg, soy, nuts, cereal or any allergenic food were sparse for individual comparisons, but showed no evidence of an association with wheeze or (for cow’s milk) lung function.</td>
</tr>
<tr>
<td><strong>Eczema Intervention</strong></td>
<td>12 RCT, 1 qRCT, 4 CCT</td>
<td>Europe, 6 North America, 3 Asia-Pacific</td>
<td>16 Cow’s milk, 10 Soya, 5 Egg, 6 Fish, 2 Peanut, 2 Wheat, 3 Tree Nuts, 6 Multifaceted studies</td>
<td>11 Doctor Diagnosis, 2 Parent Reported Symptoms, 2 Parent Report of Doctor Diagnosis, 2 Unclear</td>
<td>12 studies, ≤ 4 years; 11 studies ≤ 14 years; 1 studies ≥ 15 years</td>
<td>6,798</td>
<td>High in 8 studies (47%) due to selection bias (3), attrition bias (3) and assessment bias (2)</td>
<td>Early cow’s milk and eczema at ≤4 years RR = 1.14 (0.87 to 1.49)</td>
<td>Subgroup analyses for cow’s milk and eczema by disease risk, risk of bias, type of intervention and conflict of interest showed no group differences. Analyses were dominated by multifaceted studies, and by studies comparing cow’s milk with soya formula. Data for egg, soy, nuts, fish and wheat were sparse.</td>
</tr>
</tbody>
</table>
### Table 11. Summary of all review findings

<table>
<thead>
<tr>
<th>Report</th>
<th>Study Design</th>
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<th>Outcome Assessment</th>
<th>Age at Outcome Assessment</th>
<th>N</th>
<th>Risk of Bias</th>
<th>Main Findings</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Eczema</strong></td>
<td></td>
<td></td>
<td>ourse 29.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early cow’s milk and eczema at ≤4 years OR = 0.81 (0.63 to 1.04)</td>
<td>Subgroup analysis for cow’s milk and eczema by disease risk and risk of bias showed no group differences. Meta-analysis showed high statistical heterogeneity, and few studies adjusted for possible reverse causation. Data showed no evidence of an association with eczema.</td>
</tr>
<tr>
<td><strong>Allergic Rhinitis</strong></td>
<td>Intervention</td>
<td>34 PC, 1 NCC, 1 CC, 1 CS</td>
<td>32 Cow’s milk, 6 Soya, 17 Egg, 12 Fish, 4 Nut, 12 Cereal or Gluten, 1 Any allergenic food</td>
<td>28 Doctor Diagnosis, 7 Parent Reported Symptoms, 1 Parent Report of Doctor Diagnosis, 1 Unclear</td>
<td>30 studies, ≤ 4 years; 5 studies 5 to 14 years; 1 studies ≥ 15 years</td>
<td>59,120</td>
<td>High in 16 studies (43%) due to confounding bias (12) and selection bias (5)</td>
<td>Early egg and eczema at ≤4 years OR = 0.86 (0.58 to 1.28)</td>
<td></td>
</tr>
<tr>
<td><strong>Allergic Rhinitis</strong></td>
<td>Intervention</td>
<td>10 RCT, 3 CCT</td>
<td>13 Cow’s milk, 8 Soya, 2 Egg, 1 Fish, 3 Peanut, 2 Wheat, 1 Tree Nuts, 3 Multifaceted studies</td>
<td>1 Doctor Diagnosis, 4 Parent Reported Symptoms, 4 Parent Report of Doctor Diagnosis, 1 Unclear</td>
<td>5 studies, ≤ 4 years; 10 studies 5 to 14 years; 1 studies ≥ 15 years</td>
<td>6,333</td>
<td>High in 6 studies (46%) due to selection bias (2), attrition bias (3) and assessment bias (2)</td>
<td>Early cow’s milk and rhinitis at ≤4 years RR = 1.52 (0.97 to 2.37)</td>
<td>Subgroup analyses for cow’s milk and rhinitis by disease risk, risk of bias, type of intervention and conflict of interest showed no group differences. Analyses were dominated by multifaceted studies, and by studies comparing cow’s milk with soya formula. Data for egg, soya, nuts, fish and wheat were sparse.</td>
</tr>
<tr>
<td><strong>Allergic Rhinitis</strong></td>
<td>Observational</td>
<td>11 PC, 1 CS</td>
<td>10 Cow’s milk, 1 Soya, 1 Egg, 2 Fish, 0 Nut, 1 Cereal or Gluten</td>
<td>8 Doctor Diagnosis, 5 Parent Reported Symptoms, 0 Parent Report of Doctor Diagnosis</td>
<td>9 studies, ≤ 4 years; 4 studies 5 to 14 years; 3 studies ≥ 15 years</td>
<td>25,147</td>
<td>High in 6 studies (50%) due to confounding bias (4) and selection bias (2)</td>
<td>Early fish and rhinitis at ≤4 years OR = 0.59 (0.40 to 0.87)</td>
<td>There was no consistent evidence for an association between cow’s milk introduction and allergic rhinitis, but most studies could not be combined in meta-analysis. Data for egg, soya and cereal were sparse, but showed no evidence of an association with allergic rhinitis. There were no data for nuts.</td>
</tr>
</tbody>
</table>

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### Table 11. Summary of all review findings

<table>
<thead>
<tr>
<th>Study Design</th>
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<th>Risk of Bias</th>
<th>Main Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic Sensitization Intervention</strong></td>
<td>14 RCT, 1 qRCT, 2 CCT</td>
<td>Europe, North America, Asia Pacific</td>
<td>12 Cow’s milk, 6 Soya, 9 Egg, 7 Fish, 4 Peanut, 3 Wheat, 3 Tree Nuts</td>
<td>14 skin prick tests, 8 specific IgE antibody tests, 10 egg, 8 cow’s milk, 3 aeroallergens, 3 peanut</td>
<td>7,310</td>
<td>High in 5 studies (33%) due to selection bias (2) and attrition bias (3)</td>
<td>Early egg and sensitization to egg RR = 0.77 (0.53 to 1.11)</td>
<td>Analyses were dominated by multifaceted studies and a multiple allergic food intervention trial. Subgroup analyses showed a significant difference in outcome between multifaceted studies and other intervention trials, for early cow’s milk. Data for egg, soya, nuts, fish and wheat were sparse.</td>
</tr>
<tr>
<td><strong>Allergic Sensitization Observational</strong></td>
<td>19 PC, 1 CS</td>
<td>Europe, North America, Asia Pacific, Middle East, Latin America</td>
<td>12 Cow’s milk, 2 Soya, 7 Egg, 4 Fish, 3 Nut, 3 Cereal or Gluten, 1 Any allergenic food</td>
<td>10 skin prick tests, 8 specific IgE antibody tests, 3 only total IgE, 4 egg, 4 cow’s milk, 7 aeroallergens, 4 peanut</td>
<td>23,466</td>
<td>High in 5 studies (25%) due to confounding bias (1) and selection bias (4)</td>
<td>Early cow’s milk and sensitization to cow’s milk OR = 1.80 (0.37 to 8.70) Early egg and sensitization to egg OR = 0.82 (0.56 to 1.20)</td>
<td>Three cohort studies, with 13,472 participants reported early fish was associated with reduced sensitization to any allergen or food allergens. There was no evidence for an association between the introduction of other foods and allergic sensitization.</td>
</tr>
</tbody>
</table>
Table 11. Summary of all review findings

<table>
<thead>
<tr>
<th>Report</th>
<th>Study Design</th>
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<th>Main Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food Allergy Intervention</strong></td>
<td>12 RCT, 2 qRCT, 1 CCT</td>
<td>8 Europe, 2 North America, 5 Asia Pacific</td>
<td>9 Cow’s milk, 3 Soy, 9 Egg, 4 Fish, 3 Peanut, 3 Wheat, 2 Tree Nuts, 3 Multifaceted studies</td>
<td>6 Doctor Diagnosis, 1 Parent Reported Symptoms, 9 Food Challenge</td>
<td>12 studies, ≤ 4 years; 6 studies 5 to 14 years; 1 studies ≥ 15 years</td>
<td>10,304</td>
<td>High in 6 studies (40%) due to selection bias (4) and attrition bias (2)</td>
<td>Early egg and egg allergy at ≤4 years RR = 0.56 (0.36 to 0.87)</td>
<td>There was no evidence for a relationship between the introduction of other allergenic foods and food allergy, or between the introduction of one allergenic food and allergy to a different food.</td>
</tr>
<tr>
<td><strong>Food Allergy Observational</strong></td>
<td>13 PC, 1 RC, 3 CC, 1 NCC</td>
<td>11 Europe, 4 North America, 2 Asia Pacific, 1 Africa</td>
<td>12 Cow’s milk, 4 Soy, 5 Egg, 5 Fish, 4 Nut, 3 Cereal or Gluten, 2 Any allergenic food</td>
<td>4 Doctor Diagnosis, 6 Parent Reported Symptoms, 7 Food Challenge, 1 Unclear</td>
<td>14 studies, ≤ 4 years; 3 studies 5 to 14 years; no studies ≥ 15 years</td>
<td>40,194</td>
<td>High in 11 studies (58%) due to confounding bias (8), selection bias (4) and assessment bias (2)</td>
<td>Early egg and egg allergy at ≤4 years OR = 0.29 (0.15 to 0.56)</td>
<td>There was no evidence for a relationship between the introduction of cow’s milk, soya, fish, nuts or wheat and food allergy to these foods, or between the introduction of one allergenic food and allergy to a different food.</td>
</tr>
<tr>
<td><strong>Type 1 Diabetes Mellitus and Other Autoimmune Disease Intervention</strong></td>
<td>4 RCT, 1 qRCT</td>
<td>4 Europe, 1 North America</td>
<td>1 Cow’s milk, 4 Gluten</td>
<td>1 Clinical Diabetes, 1 Serological Diabetes, 2 Clinical Celiac Disease, 2 Serological Celiac Disease</td>
<td>2 studies, ≤ 4 years; 3 studies 5 to 14 years; no studies ≥ 15 years</td>
<td>5,623</td>
<td>High in 1 study (20%) due to attrition bias</td>
<td>Early gluten and type 1 diabetes mellitus RR = 0.71 (0.26 to 1.95)</td>
<td>There was no evidence that brief early cow’s milk exposure, or gluten introduction at age 4-6 months were associated with type 1 diabetes, and no evidence for an interaction between gluten introduction and breastfeeding status for celiac disease.</td>
</tr>
</tbody>
</table>
## eTable 11. Summary of all review findings

<table>
<thead>
<tr>
<th>Report</th>
<th>Study Design</th>
<th>Setting</th>
<th><strong>Interventions Assessed</strong></th>
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<th>Main Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 Diabetes Mellitus Observational</strong></td>
<td>8 PC, 1 NCC, 26 CC</td>
<td>23 Europe, 3 North America, 5 Asia Pacific, 3 Latin America, 1 Africa</td>
<td>33 Cow’s milk, 2 Soya, 6 Egg, 2 Fish, 0 Nut, 10 Cereal or Gluten</td>
<td>28 Clinical Diabetes, 7 Serological Diabetes</td>
<td>6 studies, ≤ 4 years; 19 studies 5 to 14 years; 16 studies ≥ 15 years</td>
<td>High in 17 studies (47%) due to confounding bias (8), selection bias (5) and assessment bias (12)</td>
<td>Early cow’s milk and type 1 diabetes, prospective studies OR = 0.92 (0.75 to 1.13)</td>
<td>There was no evidence that soya, egg, fish or cereal introduction were associated with risk of type 1 diabetes mellitus.</td>
</tr>
<tr>
<td><strong>Other Autoimmune Disease Observational</strong></td>
<td>2 SR, 4 PC, 1 NCC, 8 CC</td>
<td>9 Europe, 2 North America, 1 Asia Pacific, 1 Unclear</td>
<td>5 Cow’s milk, 8 Cereal or Gluten</td>
<td>9 Clinical Celiac Disease, 3 Serological Celiac Disease, 1 Crohn Disease, 1 Ulcerative Colitis, 2 Juvenile Idiopathic Arthritis</td>
<td>2 studies, ≤ 4 years; 4 studies 5 to 14 years; 7 studies ≥ 15 years</td>
<td>High in 5 studies (36%) due to confounding bias (3) and selection bias (3)</td>
<td>Early cow’s milk and celiac disease OR = 1.2 (0.69 to 2.1)</td>
<td>There was no evidence for an association between gluten and celiac disease, Crohn disease or ulcerative colitis, and no evidence for an interaction between gluten and breastfeeding status, and celiac disease.</td>
</tr>
</tbody>
</table>

RCT randomised controlled trial; qRCT quasi randomised controlled trial; CCT controlled clinical trial; PC prospective cohort study; RC retrospective cohort study; NCC nested case-control study; CC case control study; CS cross-sectional study; SR systematic review; OR odds ratio; RR risk ratio. aThese columns include domains that are not mutually exclusive, so that the total number reported may be greater than the total number of studies included. bThe detailed results for the findings reported in this column are available in the full report www.food.gov.uk/science/research/allergy-research/fs305005. cMultifaceted studies include at least 2 interventions other than changing the timing of allergenic food introduction in the intervention (but not control) group, for example advice regarding timing of complementary food introduction, breastfeeding advice, smoking advice, environmental control measures or maternal dietary restrictions during pregnancy or lactation.
Results of the literature search and screening procedures for recent high quality systematic reviews are shown. Revised A MeaSurement Tool to Assess systematic Reviews (R-AMSTAR) scores can range from 11 to 44, with a higher score indicating a higher quality systematic review.
Results of the literature search and screening procedures for original studies are shown. This systematic review is one of a series of reviews evaluating dietary exposures during pregnancy, lactation and infancy, and risk of allergic or autoimmune disease. These titles contained information relevant to other reviews in the series, but no information about timing of introduction of allergenic foods to the infant diet.
eFigure 3. Early allergenic food introduction and food allergy: sensitivity analyses

### A

**Study** | **Early** | **Late** | **Food Allergy** | **RR** | **95%-CI** | **W(random)**
--- | --- | --- | --- | --- | --- | ---
**Outcome = Egg Allergy** |  |  |  |  |  |  
Perkin 2016 (49) |  |  |  | 0.69 | [0.40; 1.18] | 41.4%  
Tan 2016 (51) |  |  |  | 0.59 | [0.25; 1.37] | 16.8%  
Palmer 2013 (48) |  |  |  | 0.65 | [0.38; 1.11] | 41.8%  
**Random effects model** |  |  |  | 0.65 | [0.46; 0.92] | 100%  

**Outcome = Peanut Allergy** |  |  |  |  |  |  
Perkin 2016 (49) | 7 | 571 | 15 | 597 | 0.49 | [0.20; 1.19] | 45%  
Du Toit 2015 (33) | 10 | 312 | 54 | 313 | 0.19 | [0.10; 0.36] | 55%  
**Random effects model** | 883 | 910 |  |  | 0.29 | [0.11; 0.74] | 100%  

**Outcome = Milk Allergy** |  |  |  |  |  |  
Perkin 2016 (49) | 3 | 569 | 4 | 597 | 0.79 | [0.18; 3.50] | 32.7%  
Lowe 2011 (45) | 6 | 193 | 8 | 191 | 0.74 | [0.26; 2.10] | 67.3%  
**Random effects model** | 762 | 788 |  |  | 0.76 | [0.32; 1.78] | 100%

Sensitivity analysis of effect of early versus late dietary introduction of allergenic food (egg, milk or peanut) on risk of food allergy to the same food, with abstract publications (A) or studies at unclear risk of bias (B) excluded. There were no studies at high risk of bias. The sizes of the data markers relate to study weights in the meta-analyses.
Sensitivity analysis of effect of early versus late dietary introduction of allergenic food (egg, milk or peanut) on risk of allergic sensitization to the same food, with abstract publications (A) or studies at unclear risk of bias (B) excluded. There were no studies at high risk of bias. The sizes of the data markers relate to study weights in the meta-analyses.
### eFigure 5. Early fish introduction and allergic rhinitis: sensitivity analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Age at Outcome = Birth to 4 years</th>
<th>Events</th>
<th>Total</th>
<th>Allergic Rhinitis</th>
<th>OR</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim 2011 (64)</td>
<td>246</td>
<td>4465</td>
<td></td>
<td>0.49 [0.27; 0.89]</td>
<td>30.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kull 2006 (90)</td>
<td>373</td>
<td>3575</td>
<td></td>
<td>0.77 [0.61; 0.97]</td>
<td>69.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.67 [0.45; 1.01]</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $I^2$-squared=47.8%, $p=0.1662$

<table>
<thead>
<tr>
<th>Study</th>
<th>Age at Outcome = 5 to 14 years</th>
<th>Events</th>
<th>Total</th>
<th>Allergic Rhinitis</th>
<th>OR</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nwaru 2013 (105)</td>
<td>442</td>
<td>3112</td>
<td></td>
<td>0.68 [0.47; 0.98]</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity analysis of the association between early fish introduction and odds of allergic rhinitis, with publications at high risk of bias excluded. There were no studies at unclear risk of bias. The size of the data markers relates to study weights in the meta-analysis.
eFigure 6. Early gluten introduction and celiac disease: sensitivity analyses

A

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Events</th>
<th>Late Events</th>
<th>Celiac Disease</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vriezinga 2014 (156)</td>
<td>44</td>
<td>36</td>
<td>1.2</td>
<td>[0.78; 1.82]</td>
<td></td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Events</th>
<th>Late Events</th>
<th>Celiac Disease</th>
<th>RR</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyerlein 2014 (152)</td>
<td>14</td>
<td>8</td>
<td>1.66</td>
<td>[0.74; 3.72]</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Lionetti 2014 (154)</td>
<td>53</td>
<td>64</td>
<td>0.96</td>
<td>[0.69; 1.33]</td>
<td>55.8%</td>
<td></td>
</tr>
<tr>
<td>Vriezinga 2014 (156)</td>
<td>44</td>
<td>36</td>
<td>1.20</td>
<td>[0.78; 1.82]</td>
<td>34.7%</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: I-squared=0%, p=0.4028

Sensitivity analysis of effect of early versus late dietary introduction of gluten on risk of celiac disease, with publications at high or unclear risk of bias excluded (A) or only publications at high risk of bias excluded (B). In eFigure 6 B, the size of the data markers relates to study weights in the meta-analysis.
eFigure 7. *Post hoc* Trial Sequential Analysis of moderate or high certainty review findings

**A**

- Cumulative Z-Score
- Monitoring boundary for benefit
- Optimal heterogeneity-adjusted information size = 8643 patients

**B**

- Cumulative Z-Score
- Monitoring boundary for benefit
- Optimal information size = 5239 patients
Trial sequential analysis of 6 intervention trials evaluating the effect of early dietary introduction of egg on risk of egg allergy using heterogeneity-adjusted (A) and non-adjusted (B) information sizes; and 4 intervention trials evaluating the effect of early gluten on risk of celiac disease using heterogeneity-adjusted (C) and non-adjusted (D) information sizes. There were insufficient data to conduct TSA for the meta-analysis of peanut introduction and peanut allergy. This form of analysis is designed to quantify statistical reliability of data in a cumulative meta-analysis, in a similar way to an interim analysis in a single randomized clinical trial. The vertical red line is the optimal information size i.e. the cumulative sample size required to establish with 95% 2-sided confidence whether the intervention reduces risk of the outcome by ≥30%. Horizontal green lines are z scores of +1.96 (A, B) or -1.96 (C, D), equal to two-sided P=0.05. The cumulative Z-statistic (blue line) approaches, but does not cross the trial sequential monitoring boundary (curved red line), or the futility boundary (Figure 4D) indicating no clear evidence for ≥30% relative risk reduction (A, B, C) and no clear evidence that further trials are futile (D). The datapoints on the blue (Z-statistic) and curved red (monitoring boundary) lines represent individual studies in the following order: for Figures A and B Palmer et al 201348, Bellach et al 201523, Natsume et al 201647, Palmer et al 2016221, Perkin et al 201649 and Tan et al 201651. For Figures C and D these are Sellitto et al 2012155, Beyerlein et al 2014152, Lionetti et al 2014154 and Vriezinga et al 2014156.
References


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.
rye, barley, oat, root, tuber, exp Cereals/
exp Vegetables/
vegetable, onion, spinach, chard, tomato, pepper, carrot, beetroot, asparagus, garlic, pumpkin, sprouts, broccoli, cabbage, celery, ginger, potato, crisps, fries, syrup, honey, Honey/
Fruit/
fruit, apple, pear, banana, orange, grape, kiwi, citrus, grapefruit, pulses, beans, lentil, chickpea, legume, lupin, soy, soya, nut, almond, peanut, groundnut, Nuts/
Seeds/
sesame, mustard, Seeds/
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.

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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/
autoimmune disease. ab, ti.
diabetes. ab, ti.
diabetic. ab, ti.
type 1. ab, ti.
celiac disease. ab, ti.
crohn's disease. ab, ti.
Inflammatory Bowel Disease. ab, ti.
Ulcerative colitis. ab, ti.
(Lympho) adj3 thyroiditis. ab, ti.
(Thyroiditis adj3 autoimmune). ab, ti.
(Hashimoto adj3 (syndrome? or thyroiditis or disease?)). ab, ti.
(Thyroiditis adj3 (post-partum or postpartum)). ab, ti.
Graves? disease. ab, ti.
Basedow? disease. ab, ti.
exophthalmic goiter?. ab, ti.
(Still? Disease adj3 (juvenile or onset)). ab, ti.
(Juvenile adj3 arthritis). ab, ti.
vitiligo. ab, ti.
Psoriasis?. ab, ti.
Allergic dermatitis. ab, ti.
(food? adj3 sensiti$). ab, ti.
(food? adj3 tolerant$). ab, ti.
(food? adj3 intolerant$). ab, ti.
((aero or air$) adj3 allergen?). ab, ti.
(aeroallergen? adj3 sensititi$). ab, ti.
(allergen? adj3 sensititi$). ab, ti.
skin prick test$. ab, ti.
atopy. ab, ti.
hypersensitivity$. ab, ti.
exp Food Hypersensitivity/
Respiratory Hypersensitivity/
Asthma/
Bronchial Hyperreactivity/
Forced Expiratory Volume/
Vital Capacity/
Peak Expiratory Flow Rate/
Eczema/
Neurodermatitis/
Rhinitis/
Rhinitis, Allergic, Perennial/
Rhinitis, Allergic, Seasonal/
Conjunctivitis/
Immunoglobulin E/
Autoimmune Diseases/
Diabetes Mellitus, Type 1/
Celiac Disease/
Crohn Disease/
Inflammatory Bowel Diseases/
Colitis, Ulcerative/
Thyroiditis, Autoimmune/
Hashimoto Disease/
Postpartum Thyroiditis/
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 or 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.
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. 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.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>nut/</td>
</tr>
<tr>
<td>56</td>
<td>peanut/</td>
</tr>
<tr>
<td>57</td>
<td>almond/</td>
</tr>
<tr>
<td>58</td>
<td>Brazil nut/</td>
</tr>
<tr>
<td>59</td>
<td>exp walnut/</td>
</tr>
<tr>
<td>60</td>
<td>pecan/</td>
</tr>
<tr>
<td>61</td>
<td>pistachio/</td>
</tr>
<tr>
<td>62</td>
<td>cashew nut/</td>
</tr>
<tr>
<td>63</td>
<td>hazelnut/</td>
</tr>
<tr>
<td>64</td>
<td>Corylus avellana/</td>
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<tr>
<td>65</td>
<td>Macadamia/</td>
</tr>
<tr>
<td>66</td>
<td>wheat.ti,ab.</td>
</tr>
<tr>
<td>67</td>
<td>exp wheat/</td>
</tr>
<tr>
<td>68</td>
<td>soya.ti,ab.</td>
</tr>
<tr>
<td>69</td>
<td>soybean/</td>
</tr>
<tr>
<td>70</td>
<td>gluten$.ti,ab.</td>
</tr>
<tr>
<td>71</td>
<td>gluten/</td>
</tr>
<tr>
<td>72</td>
<td>fish$.ti,ab.</td>
</tr>
<tr>
<td>73</td>
<td>fish/</td>
</tr>
<tr>
<td>74</td>
<td>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</td>
</tr>
<tr>
<td>75</td>
<td>diet/</td>
</tr>
<tr>
<td>76</td>
<td>diet therapy/</td>
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<tr>
<td>77</td>
<td>nutritional science/</td>
</tr>
<tr>
<td>78</td>
<td>diet.ti,ab.</td>
</tr>
<tr>
<td>79</td>
<td>diets.ti,ab.</td>
</tr>
<tr>
<td>80</td>
<td>Mediterranean diet/</td>
</tr>
<tr>
<td>81</td>
<td>mediterranean diet$.ab,ti.</td>
</tr>
<tr>
<td>82</td>
<td>dietetic.ab,ti.</td>
</tr>
<tr>
<td>83</td>
<td>dietary.ab,ti.</td>
</tr>
<tr>
<td>84</td>
<td>eat.ab,ti.</td>
</tr>
<tr>
<td>85</td>
<td>eating.ab,ti.</td>
</tr>
<tr>
<td>86</td>
<td>intake.ab,ti.</td>
</tr>
<tr>
<td>87</td>
<td>nutrient?.ab,ti.</td>
</tr>
<tr>
<td>88</td>
<td>nutrition.ab,ti.</td>
</tr>
<tr>
<td>89</td>
<td>vegetarian diet/</td>
</tr>
<tr>
<td>90</td>
<td>vegetarian?.ti,ab.</td>
</tr>
<tr>
<td>91</td>
<td>vegan$.ti,ab.</td>
</tr>
<tr>
<td>92</td>
<td>macrobiotic diet/</td>
</tr>
<tr>
<td>93</td>
<td>macrobiotic?.ti,ab.</td>
</tr>
<tr>
<td>94</td>
<td>food/</td>
</tr>
<tr>
<td>95</td>
<td>food$.ab,ti.</td>
</tr>
<tr>
<td>96</td>
<td>feed.ab,ti.</td>
</tr>
<tr>
<td>97</td>
<td>feeding.ab,ti.</td>
</tr>
<tr>
<td>98</td>
<td>cereal$.ab,ti.</td>
</tr>
<tr>
<td>99</td>
<td>grain$.ab,ti.</td>
</tr>
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<td>100</td>
<td>granary.ab,ti.</td>
</tr>
<tr>
<td>101</td>
<td>wholegrain.ab,ti.</td>
</tr>
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<td>102</td>
<td>wholewheat.ab,ti.</td>
</tr>
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<td>103</td>
<td>whole wheat.ab,ti.</td>
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<tr>
<td>104</td>
<td>wheat.ab,ti.</td>
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<tr>
<td>105</td>
<td>wheatgerm.ab,ti.</td>
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<td>106</td>
<td>rye.ab,ti.</td>
</tr>
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<td>107</td>
<td>barley.ab,ti.</td>
</tr>
<tr>
<td>108</td>
<td>oat?.ab,ti.</td>
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</tbody>
</table>
1078 109. exp cereal/
1079 110. root?.ti,ab.
1080 111. tuber?.ti,ab.
1081 112. exp vegetable/
1082 113. vegetable$.ab,ti.
1083 114. onion$.ab,ti.
1084 115. spinach.ab,ti.
1085 116. chard.ab,ti.
1086 117. tomato$.ab,ti.
1087 118. pepper$.ab,ti.
1088 119. carrot$.ab,ti.
1089 120. beetroot.ab,ti.
1090 121. asparagus.ab,ti.
1091 122. garlic.ab,ti.
1092 123. pumpkin.ab,ti.
1093 124. sprouts.ab,ti.
1094 125. broccoli.ab,ti.
1095 126. cabbage$.ab,ti.
1096 127. celery.ab,ti.
1097 128. ginger.ab,ti.
1098 129. potato$.ab,ti.
1099 130. crisps.ab,ti.
1100 131. fries.ab,ti.
1101 132. syrup.ab,ti.
1102 133. honey.ab,ti.
1103 134. honey/
1104 135. fruit/
1105 136. fruit$.ab,ti.
1106 137. apple?.ab,ti.
1107 138. pear?.ab,ti.
1108 139. banana?.ab,ti.
1109 140. orange?.ab,ti.
1110 141. grape?.ab,ti.
1111 142. kiwi?.ab,ti.
1112 143. citrus.ab,ti.
1113 144. grapefruit?.ab,ti.
1114 145. pulses.ab,ti.
1115 146. beans.ab,ti.
1116 147. lentil?.ab,ti.
1117 148. chickpea?.ab,ti.
1118 149. legume?.ab,ti.
1119 150. lupin?.ab,ti.
1120 151. soy.ab,ti.
1121 152. soya.ab,ti.
1122 153. nut?.ab,ti.
1123 154. almond?.ab,ti.
1124 155. peanut?.ab,ti.
1125 156. groundnut?.ab,ti.
1126 157. exp nut/
1127 158. seed?.ti,ab.
1128 159. sesame.ti,ab.
1129 160. mustard.ti,ab.
1130 161. plant seed/
1131 162. meat/
1132 163. meat.ab,ti.
1133 164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. fatty acid/
173. omega 3 fatty acid/
174. omega 6 fatty acid/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats,ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs,ab,ti.
183. exp egg/
184. bread/
185. bread,ti,ab.
186. oil,ti,ab.
187. oils,ti,ab.
188. oily,ti,ab.
189. omega,ti,ab.
190. sea food/
191. seafood,ti,ab.
192. shellfish,ti,ab.
193. crustacean?,ti,ab.
194. molluse?,ti,ab.
195. shellfish/
196. exp dairy product/
197. dairy,ti,ab.
198. milk/
199. milk,ti,ab.
200. artificial milk/
201. formula?,ti,ab.
202. hydrolysed,ti,ab.
203. baby food/
204. yoghurt,ab,ti.
205. probiotic,ab,ti.
206. prebiotic?,ab,ti.
207. butter,ab,ti.
208. herb?,ab,ti.
209. spice?,ab,ti.
210. chilli$,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.
dietary proteins, protein intake, animal protein, total protein, vegetable protein, plant protein, carbohydrate diet, carbohydrate intake, fat intake, dietary fiber, protein intake, diet supplementation, food additive, exp vitamin, supplements, supplement, vitamin, retinol, carotenoid, tocopherol, folate, folic acid, methionine, riboflavin, thiamine, niacin, pyridoxine, cobalamin, mineral, sodium, iron, calcium, selenium, iodine, magnesium, potassium, zinc, copper, phosphorus, manganese, chromium, phytochemical, polyphenol, phytoestrogen, genistein, saponin, coumarin, flavonoid, ascorbic acid, hydroxy cholecalciferol, hydroxycholecalciferol.

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1302 333. tocoptrienol$.ab,ti.
1303 334. carotene$.ab,ti.
1304 335. cryptoxanthin$.ab,ti.
1305 336. lycopene$.ab,ti.
1306 337. lutein$.ab,ti.
1307 338. zeaxanthin$.ab,ti.
1308 339. selenium$.ab,ti.
1309 340. organic diet?.ab,ti.
1310 341. organic food/
1311 342. 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or
1312 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111
1313 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or
1314 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or
1315 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or
1316 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or
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1325 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or
1326 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or
1327 336 or 337 or 338 or 339 or 340 or 341
1328 342. allerg$.ab,ti.
1329 344. asthma$.ab,ti.
1330 345. wheeze.ab,ti.
1331 346. wheezing.ab,ti.
1332 347. bronchial hyperresponsiveness.ab,ti.
1333 348. bronchial hyperreactivity.ab,ti.
1334 349. Forced expiratory volume.ab,ti.
1335 350. FEV1.ab,ti.
1336 351. "FEV 1".ab,ti.
1337 352. "FEV0.5".ab,ti.
1338 353. "FEV 0.5".ab,ti.
1339 354. Forced vital capacity.ab,ti.
1340 355. FVC.ab,ti.
1341 356. Peak expiratory flow rate.ab,ti.
1342 357. PEFR.ab,ti.
1343 358. eczema.ab,ti.
1344 359. neurodermatitis.ab,ti.
1345 360. rhinitis.ab,ti.
1346 361. besniers prurigo.ab,ti.
1347 362. rhinoconjunctivitis.ab,ti.
1348 363. hayfever.ab,ti.
1349 364. (hay adj fever).ab,ti.
1350 365. poll?nosis.ab,ti.
1351 366. SAR.ab,ti.
1352 367. (pollen adj allergy).ab,ti.
1353 368. conjunctivitis.ab,ti.
1354 369. immunoglobulin e.ab,ti.
1355 370. Total IgE.ab,ti.
1356 371. autoimmune disease?.ab,ti.
1357 372. diabetes.ab,ti.
373. diabetic.ab,ti.
374. type 1.ab,ti.
375. celiac disease.ab,ti.
376. crohn$ 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.
384. Basedow$ disease.ab,ti.
385. exophthalmic goiter?.ab,ti.
386. (Still? Disease adj3 (juvenile or onset)).ab,ti.
387. (Juvenile adj3 arthriti$).ab,ti.
388. vitiligo.ab,ti.
389. Psoriasis?.ab,ti.
391. atopic disease.ab,ti.
392. atopic dermatitis,ab,ti.
393. (food? adj3 sensiti$).ab,ti.
396. ((aero or air$) adj3 allergen?).ab,ti.
397. (aeroallergen? adj3 sensiti$).ab,ti.
399. skin prick test$.ab,ti.
400. atopy.ab,ti.
401. hypersensitiv$.ab,ti.
402. exp hypersensitivity/
403. respiratory tract allergy/
404. asthma/
405. wheezing/
406. bronchus hyperreactivity/
407. forced expiratory volume/
408. forced vital capacity/
409. peak expiratory flow/
410. eczema/
411. neurodermatitis/
412. rhinitis/
413. rhinoconjunctivitis/
414. hay fever/
415. pollen allergy/
416. perennial rhinitis/
417. conjunctivitis/
418. immunoglobulin E/
419. autoimmune disease/
420. diabetes mellitus/
421. insulin dependent diabetes mellitus/
422. celiac disease/
423. Crohn disease/
424. enteritis/
425. ulcerative colitis/
426. autoimmune thyroiditis/
427. Hashimoto disease/
428. postpartum thyroiditis/
Graves disease/
juvenile rheumatoid arthritis/
vitiligo/
psoriasis/
psoriatic arthritis/
atopic dermatitis/
nutritional intolerance/
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
infant?.ab,ti.
((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.
((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.
438 or 439
(old or age?).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.
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

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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
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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
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
342. 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
343. 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
344. 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
345. 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
346. 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
347. 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
348. 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
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350. 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
351. 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
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354. 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
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356. 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
357. 335 or 336 or 337 or 338 or 339 or 340
358. allerg*:ab,ti
359. asthma*:ab,ti
360. wheeze:ab,ti
361. wheezing:ab,ti
362. “bronchial hyperresponsiveness”*:ab,ti
363. “bronchial hyperreactivity”:ab,ti
364. “Forced expiratory volume”:ab,ti
365. “FEV1”:ab,ti
366. "FEV 1":ab,ti
367. "FEV0.5":ab,ti
368. "FEV 0.5":ab,ti
369. “Forced vital capacity”:ab,ti
370. FVC:ab,ti
371. PEFR:ab,ti
372. eczema:ab,ti
373. neurodermatitis:ab,ti
374. rhinitis:ab,ti
375. “besnier’s prurigo”:ab,ti
376. rhinoconjunctivitis:ab,ti
377. hayfever:ab,ti
378. hay fever*:ab,ti
379. poll*nosis:ab,ti
380. poll*enosis:ab,ti
381. SAR:ab,ti
382. “pollen allergy”:ab,ti
383. conjunctivitis:ab,ti
384. immunoglobulin e:ab,ti
385. Total IgE:ab,ti
386. “autoimmune disease*”:ab,ti
387. diabetes:ab,ti
388. 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. atop: ab, ti
400. hypersensitiv*: ab, ti
401. MeSH descriptor [Hypersensitivity] this term only
402. MeSH descriptor [Food Hypersensitivity] explode all trees
403. MeSH descriptor [Respiratory Hypersensitivity] this term only
404. MeSH descriptor [Asthma] this term only
405. MeSH descriptor [Bronchial Hyperreactivity] this term only
406. MeSH descriptor [Forced Expiratory Volume] this term only
407. MeSH descriptor [Vital Capacity] this term only
408. MeSH descriptor [Peak Expiratory Flow Rate] this term only
409. MeSH descriptor [Eczema] this term only
410. MeSH descriptor [Neurodermatitis] this term only
411. MeSH descriptor [Rhinitis] this term only
412. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
413. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
414. MeSH descriptor [Conjunctivitis] this term only
415. MeSH descriptor [Immunoglobulin E] this term only
416. MeSH descriptor [Autoimmune Diseases] this term only
417. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
418. MeSH descriptor [Celiac Disease] this term only
419. MeSH descriptor [Crohn Disease] this term only
420. MeSH descriptor [Inflammatory Bowel Diseases] this term only
421. MeSH descriptor [Colitis, Ulcerative] this term only
422. MeSH descriptor [Thyroiditis, Autoimmune] this term only
423. MeSH descriptor [Hashimoto Disease] this term only
424. MeSH descriptor [Postpartum Thyroiditis] this term only
425. MeSH descriptor [Graves Disease] this term only
426. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
427. MeSH descriptor [Vitiligo] this term only
428. MeSH descriptor [Psoriasis] this term only
429. MeSH descriptor [Arthritis, Psoriatic] this term only
430. MeSH descriptor [Dermatitis, Atopic] this term only
431. MeSH descriptor [Hypersensitivity, Immediate] this term only
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
432. infant*:ab,ti
433. ((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
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") NEAR/1 month*:ab,ti
435. (maternal NEAR/7 pregnan*):ab,ti
436. (mother* NEAR/7 pregnan*):ab,ti
437. (old or age*):ab,ti
438. 432 and 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 pregman*: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
449. Publication date from 2011
100
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Appendix 2 Search Strategies for original articles (Review B)

2.1. Medline

1. complementary food?.ab,t.
2. (introduc$ adj2 food$).ab,t.
3. wean$.ab,t.
4. Weaning/
5. solid?.ab,t.
6. semi-solid?.ab,t.
7. baby food?.ab,t.
8. Infant Food/
9. Infant Nutritional Physiological Phenomena/
10. breast feeding,ab,t.
11. breastfeeding,ab,t.
12. breast fed,ab,t.
13. breastfed,ab,t.
14. Breast Feeding/
15. Milk, Human/
16. formula?,ab,t.
17. hydrolysed,ab,t.
18. bottlefed,ab,t.
19. bottle fed,ab,t.
20. (bottle adj3 feed$).ab,t.
21. Infant Formula/
22. Bottle Feeding/
23. liquid?,ab,t.
24. milk,ab,t.
25. Milk/
26. egg?,ab,t.
27. Egg Proteins/
28. Egg Proteins, Dietary/
29. nut?,ab,t.
30. peanut?,ab,t.
31. almond?,ab,t.
32. (brazil? adj5 nut?).ab,t.
33. walnut?,ab,t.
34. pecan?,ab,t.
35. pistachio?,ab,t.
36. cashew?,ab,t.
37. hazelnut?,ab,t.
38. macadamia?,ab,t.
39. Nuts/
40. Arachis hypogaea/
41. Prunus/
42. Bertholletia/
43. Juglans/
44. Carya/
45. Pistacia/
46. Anacardium/
47. Corylus/
48. Macadamia/
49. wheat,ab,t.
50. Triticum/
51. soya,ab,t.
52. Soybeans/
1987  53. gluten$.ab,ti.
1988  54. Glutens/
1989  55. fish.ab,ti.
1990  56. Fishes/
1991  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
1992  58. 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
1993  59. allerg$.ab,ti.
1994  60. asthma$.ab,ti.
1995  61. wheeze.ab,ti.
1996  62. bronchial hyperresponsiveness.ab,ti.
1997  63. bronchial hyperreactivity.ab,ti.
2000  64. Forced expiratory volume.ab,ti.
2001  65. FEV1.ab,ti.
2002  66. "FEV 1".ab,ti.
2003  67. "FEV0.5".ab,ti.
2004  68. "FEV 0.5".ab,ti.
2005  69. Forced vital capacity.ab,ti.
2006  70. FVC.ab,ti.
2007  71. Peak expiratory flow rate.ab,ti.
2008  72. PEFR.ab,ti.
2009  73. eczema.ab,ti.
2010  74. neurodermatitis.ab,ti.
2011  75. rhinitis.ab,ti.
2012  76. besniers prurigo.ab,ti.
2013  77. rhinoconjunctivitis.ab,ti.
2014  78. hayfever.ab,ti.
2016  80. poll?nosis.ab,ti.
2017  81. SAR.ab,ti.
2018  82. (pollen adj allergy).ab,ti.
2019  83. conjunctivitis.ab,ti.
2020  84. immunoglobulin e.ab,ti.
2021  85. Total IgE.ab,ti.
2022  86. autoimmune disease?.ab,ti.
2023  87. diabetes.ab,ti.
2024  88. diabetic.ab,ti.
2025  89. type 1.ab,ti.
2026  90. c?eliac disease.ab,ti.
2027  91. crohn$. disease.ab,ti.
2028  92. Inflammatory Bowel Disease?.ab,ti.
2029  93. Ulcerative colitis.ab,ti.
2030  94. (Lympho$ adj3 thyroiditi$).ab,ti.
2031  95. (Thyroiditi$ adj3 autoimmune).ab,ti.
2032  96. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
2033  97. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
2036  100. exophthalmic goiter?.ab,ti.
2037  101. (Still? Disease adj3 (juvenile or onset)).ab,ti.
2038  102. (Juvenile adj3 arthriti$).ab,ti.
2039  103. vitiligo.ab,ti.
2040  104. Psorias?$.ab,ti.
2042  106. atopic disease.ab,ti.

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107. atopic dermatitis
108. (food? adj3 sensiti$)
109. (food? adj3 toleran$)
110. (food? adj3 intoleran$)
111. ((aero or air$) adj3 allergen?)
112. (aeroallergen? adj3 sensiti$)
113. (allergen? adj3 sensiti$)
114. skin prick test$
115. atopy
116. hypersensitiv$
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. Celiac 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?.
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?)
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?)
152. 150 or 151
153. (old or age?)
("one year?" or "two year?") adj3 (old or age?).ab,ti.
((first or second or two) adj3 "year? of life").ab,ti.
Infant/
Infant, Newborn/
149 or 154 or 155 or 156 or 157 or 158
clinical trial?.mp.
random$.mp.
factorial$.mp.
crossover$.mp.
placebo$.mp.
(doub$ adj blind$).mp.
(singl$ adj blind$).mp.
assign$.mp.
volunteer$.mp.
cohort stud$.mp.
longitudinal$.mp.
follow-up.mp.
prospectiv$.mp.
retrospectiv$.mp.
case control.mp.
case referent.mp.
exp clinical trial/
Cross-Over Studies/
Placebos/
Double-Blind Method/
Single-Blind Method/
exp Cohort Studies/
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.
100. Basedow$ disease,ab,ti.
101. exophthalmic goiter?,ab,ti.
102. (Still? Disease adj3 (juvenile or onset)).ab,ti.
103. (Juvenile adj3 arthriti$).ab,ti.
104. vitiligo,ab,ti.
105. Psorias?$.ab,ti.
107. atopic disease,ab,ti.
108. atopic dermatitis,ab,ti.
109. (food? adj3 sensitivi$).ab,ti. 2243
110. (food? adj3 toleranc$).ab,ti. 2244
111. (food? adj3 intoleranc$).ab,ti. 2245
112. ((aero or air$) adj3 allergen?).ab,ti. 2246
113. (aeroallergen? adj3 sensitivi$).ab,ti. 2247
114. (allergen? adj3 sensitivi$).ab,ti. 2248
115. skin prick test$.ab,ti. 2249
116. atopy.ab,ti. 2250
117. hypersensitiv$.ab,ti. 2251
118. exp hypersensitivity/ 2252
119. respiratory tract allergy/ 2253
120. asthma/ 2254
121. wheezing/ 2255
122. bronchus hyperreactivity/ 2256
123. forced expiratory volume/ 2257
124. forced vital capacity/ 2258
125. peak expiratory flow/ 2259
126. eczema/ 2260
127. neurodermatitis/ 2261
128. rhinitis/ 2262
129. rhinoconjunctivitis/ 2263
130. hay fever/ 2264
131. pollen allergy/ 2265
132. perennial rhinitis/ 2266
133. conjunctivitis/ 2267
134. immunoglobulin E/ 2268
135. autoimmune disease/ 2269
136. diabetes mellitus/ 2270
137. insulin dependent diabetes mellitus/ 2271
138. celiac disease/ 2272
139. Crohn disease/ 2273
140. enteritis/ 2274
141. ulcerative colitis/ 2275
142. autoimmune thyroiditis/ 2276
143. Hashimoto disease/ 2277
144. Graves disease/ 2278
145. juvenile rheumatoid arthritis/ 2279
146. vitiligo/ 2280
147. psoriasis/ 2281
148. psoriatic arthritis/ 2282
149. atopic dermatitis/ 2283
150. nutritional intolerance/ 2284
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 week?).ab,ti. 2285
152. ((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. 2286

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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 (Still's 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”)

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2.4. COCHRANE Library

1. “complementary food*”:ab,ti
2. (introduce* 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 [Breastfeeding] 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. “Ulcervative 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 [Celiac 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 [Graves Disease] this term only
141. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
142. MeSH descriptor [Vitiligo] this term only
143. MeSH descriptor [Psoriasis] this term only
144. MeSH descriptor [Arthritis, Psoriatic] this term only
145. MeSH descriptor [Dermatitis, Atopic] this term only
146. MeSH descriptor [Hypersensitivity, Immediate] this term only
147. 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. 152 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$ or (Arthriti$ NEAR/3 Psoria*) or “atopic disease” or “atopic dermatitis” or (food$ NEAR/3 sensiti*) or (food$ NEAR/3 tolerant*) or (food$ NEAR/3 intolera*) 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

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