Review of scientific published literature on infant feeding and development of atopic and autoimmune disease

Review A – Milk Feeding

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Introduction

This is one of 3 systematic reviews being undertaken as part of a review of the scientific literature on infant feeding and development of atopic and autoimmune diseases commissioned by the UK Food Standards Agency. Atopic conditions such as asthma, eczema, rhinoconjunctivitis and food allergy appear to have increased in prevalence in recent decades in many countries, and are now the leading causes of chronic illness during childhood in the UK. The apparently rapid changes in disease prevalence, combined with data from migration studies, suggest that early life environmental factors may be important modulators of atopic disease risk. Similar findings apply to the autoimmune diseases type I diabetes mellitus and Crohn’s disease, which also appear to have increased in prevalence in some countries. Significant attention has focussed on dietary exposures in relation to these immune-mediated atopic and autoimmune diseases for 2 reasons – first the temporal association between rises in atopic/autoimmune conditions and changing dietary exposures in the relevant populations; second the gut associated lymphoid tissue is our largest collection of immune tissue, and our most mature immune organ at the time of birth. Hence early enteral exposures are likely to be especially potent modulators of immune development and risk of immune-mediated disease. Although there are a large number of observational studies, some intervention trials and several systematic reviews in this area, they tend to focus on one specific area of diet and a limited number of immune outcomes. The purpose of these 3 systematic reviews is to comprehensively assess the existing literature regarding the relationship between maternal and infant dietary exposures and a child’s risk of any of the common atopic and autoimmune disease, in order to inform UK Department of Health feeding guidance for mothers and their infants. These protocols have been developed by the authors, but have been modified after independent expert peer review and reviews and
meetings with members of the UK Food Standards Agency and the UK Scientific Advisory Committee on Nutrition. The specific outcomes of interest for these reviews, chosen due to their high prevalence in the UK population, and described in more detail below, are: Food allergy, Eczema, Asthma, Allergic rhinitis, Allergic conjunctivitis, Allergic sensitisation, Type 1 diabetes mellitus, Coeliac disease, Inflammatory bowel disease, Autoimmune thyroid disease, Juvenile rheumatoid arthritis, Vitiligo, Psoriasis.

**Key words**

Infant; diet; breastfeed; milk; allergy; atopy; asthma; eczema; food allergy; sensitisation; rhinitis; conjunctivitis; autoimmune; diabetes; crohn; inflammatory bowel disease; coeliac; thyroiditis; juvenile arthritis; vitiligo; psoriasis; systematic review
Review question(s)

A1. Does the duration of exclusive/predominant breastfeeding during the first year of life, influence children’s future risk of atopic disease, allergic sensitisation or autoimmune disease.

A2. Does the total duration of breastfeeding up to 2 years, influence children’s future risk of atopic disease, allergic sensitisation or autoimmune disease.

A3. Does the timing of introduction of non-milk feeds (ie not breastmilk or formula milk) during the first year of life, influence children’s future risk of atopic disease, allergic sensitisation or autoimmune disease.

Inclusion Criteria

Types of study to be included

We will include randomised controlled trials (RCT), quasi RCT, and where necessary prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies or other case control studies. We will take a hierarchical approach to study design, such that where data are absent or limited from certain types of studies, we will include lower level study designs. So where high quality intervention studies are lacking, we will include prospective cohort studies; where high quality prospective cohort studies are lacking we will include retrospective cohort studies; where high quality retrospective cohort studies are lacking we will include data from nested case-control studies, and where these are lacking we will use other types of case control studies. We will not include non-comparative studies, or non-human studies.
Participants/population

Inclusion criteria: Infants between the age of 0 and the end of their 12th post-partum month (questions A1 and A3) or 0 and the end of the 24th post-partum month (question A2). If infants are characterised as high or standard risk for atopic disease based on family history, this information will be recorded so that subgroup analysis can be made.

Context

Our primary analyses will exclude studies in which participants were defined by a disease state - e.g. pregnant women with specific nutritional deficiencies, infants born prematurely (<31 weeks gestation) or other groups clearly representing <5% of the UK population, since the results of this review should apply to the general UK population. We will include studies of specific ethnic groups. Studies where subject eligibility is defined on the basis of a family history of allergy will be included, since this applies to a majority of infants in the UK. Studies restricted to populations at specific genetic risk of autoimmune disease (e.g. by HLA type) will also be included, since it is difficult to undertake studies of autoimmune disease prevention in the general population due to low prevalence.

Interventions/exposures

Review question #A1: Timing of the transition from exclusive/predominant breastfeeding (as defined by the World Health Organisation [WHO]), to partial or no breastfeeding (i.e. introduction of a complementary food including infant formula). Where possible, the exposure will be measured both as a continuous variable, and categorised as more/less than 4 months and more/less than 6 months.

- Inclusion criteria - studies which describe an analysis of duration of exclusive/predominant breastfeeding as defined by WHO, or using similar criteria, in relation to the outcomes of interest.
Exclusive breastfeeding is defined by WHO as ‘no other food or drink, not even water, except breast milk (including milk expressed or from a wet nurse) other than oral rehydration solution, and drops/syrups (vitamins, minerals and medicines)’.

Predominant breastfeeding is defined by WHO as meaning ‘the infant's predominant source of nourishment is breast milk (as defined above), but they may also receive liquids (water and water-based drinks, fruit juice) and ritual fluids in addition to those permitted under exclusive breastfeeding.’

- exclusion criteria - studies where breastfeeding duration is analysed, but the authors do not analyse or report the data in a way that can be interpreted within the WHO definition of exclusive/predominant breastfeeding.

Review question #A2: Timing of the duration of breastfeeding (ie time to complete cessation of breastfeeding). Where possible, the exposure will be measured both as a continuous variable and categorised as more/less than 6 months and more/less than 1 year.

- inclusion criteria - studies where the timing of cessation (or non-initiation) of breastfeeding is documented, up to 2 years age, and analysed in relation to the outcomes of interest.

Review question #A3: Timing of the transition from liquid infant milk feed (i.e. breast milk and/or infant formula) to the introduction of other complementary foods. Where possible, the exposure will be measured both as a continuous variable, and categorised as more/less than 4 months and more/less than 6 months.

- inclusion criteria - studies where the timing of introduction of non-milk feeds is described, in relation to the outcomes of interest.

- exclusion criteria - studies where duration of breastfeeding/timing of formula feeding is described, but timing of introduction of non-milk feeds is not described.
Comparator(s)/control

All comparators will be included, including studies which compare different doses or forms of an exposure eg different patterns of breastfeeding. We will not however include studies comparing different types of formula milk such as hydrolysed versus non-hydrolysed, or soy versus cow's milk.

Search strategy

We will search for eligible studies in MEDLINE, EMBASE, Cochrane, Web of Science and LILACS with no specified start date. We will include peer reviewed publications, and also include proceedings and abstracts presented in scientific conferences in the last 3 years, if they have not subsequently been published as a peer reviewed publication. We will search for studies in progress, or completed but unpublished studies using http://apps.who.int/trialsearch/, and will contact international experts in the field of nutritional exposures in relation to allergy and autoimmune disorders, including where appropriate pharmaceutical or food industry representatives, to identify important unpublished work. We will review the bibliography of eligible studies for possible additional publications, and will include all eligible publications, regardless of the language. Where necessary, and where feasible within the limited timescale of this project, the authors of eligible or potentially eligible studies will be contacted by the research team to obtain any data that might not be available in the abstract/publication. Potentially eligible studies are studies which have clearly recorded both an exposure and an outcome of interest, but have not reported an analysis of the relationship between these.

The MEDLINE search strategy is at the end of this document, as an Appendix.

We will separately search for existing systematic reviews which cover any of the same exposure(s)/outcome(s) as these, and were published since 1st January 2011. We will quality
assess such existing systematic reviews using the revised AMSTAR criteria\(^5\). We will not
duplicate any existing systematic reviews with revised AMSTAR score $\geq 32$, but will instead
summarise the findings of such reviews and include the summary in our final report. As far as
possible, these data will be presented using Cochrane Summary of Findings tables, generated
using GradePro. For these pre-existing, high quality systematic reviews, we will also
summarise any eligible publications identified in the searches, which were published
subsequent to the relevant systematic review, in our final report.

**Study Outcomes**

We have selected atopic and autoimmune outcomes on the basis of their population
prevalence in children and young adults in the UK or other affluent nations. We have
included diseases with a prevalence of at least 1 in 1000, in children/adolescents or young
adults (aged $<40$ years), but have not included rarer diseases\(^6\). We have not included
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. For all outcome measures, age at assessment will be grouped as 1-4
years, 5-14 years, 15-24 years, 25-44 years, 45-64 years and $\geq 65$ years. Where studies report
the same outcome at different timepoints within one of these frames, we will use the
timepoint which has the most complete dataset i.e., lowest percentage of missing data as the
primary assessment point. For each outcome measure in this review, there is more than one
possible method of assessment. We have 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. We will however document all relevant outcomes measured
using different assessment tools, in each included study. This will allow for meta-analysis of
different studies where they have used similar outcome measures.

**Atopic outcomes:**

1. **Asthma** - 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.

Primary assessment: parent or self-report using a validated questionnaire such as the
International Study of Asthma and Allergies in Childhood questionnaire 7, at 5-14 years.

Where multiple measures are used, cumulative incidence of wheezing will be used
preferentially.

2. **Eczema** – defined using parent/self report, doctor diagnosis, a validated questionnaire,
scoring system or objective measure.

Primary assessment: parent or self-report using a validated questionnaire such as the UK
adaptation of Hanifin and Rajka criteria 8 at 1-4 years. Where multiple measures are used,
cumulative incidence of eczema will be analysed preferentially, but point prevalence will also
be reported.

3. **Allergic Rhinitis** – defined using parent/self report, doctor diagnosis, a validated
questionnaire, scoring system or objective measure.

Primary assessment: parent or self-report using a validated questionnaire such as the
International Study of Asthma and Allergies in Childhood questionnaire 7, at 5-14 years.

Where multiple measures are used, cumulative incidence will be analysed preferentially.

4. **Allergic Conjunctivitis** - defined using parent/self report, doctor diagnosis, a validated
questionnaire, scoring system or objective measure.
Primary assessment: parent or self-report using a validated questionnaire, at 5-14 years.

Where multiple measures are used, cumulative incidence will be analysed preferentially.

5. Food allergy - defined by double blind placebo controlled food challenge, by open food challenge, by medical diagnosis or by self/parent report.

Primary assessment: challenge-proven food allergy, assessed at 1-4 years. Where multiple measures are used, cumulative incidence will be analysed preferentially.

6. Allergic sensitisation – to an inhalant, an ingestant, or both – defined as positive skin prick test and/or specific IgE test to the relevant allergen using recognised methodologies and scoring criteria.

Primary assessment: sensitisation to at least one inhalant or ingestant, assessed at 5-14 years or older. Where multiple measures are used, point prevalence will be analysed preferentially.

7. Total IgE – measured using a recognised technology such as ImmunoCAP (ThermoFisher, Massachusetts).

Autoimmune outcomes:

1. Type I diabetes mellitus – defined as a medical diagnosis, or a surrogate marker such as autoantibodies against insulin, GAD65, IA-2 or the ZnT8 transporter in the first 3 years of life.

Primary assessment: medical diagnosis of type 1 diabetes mellitus using the 1999 WHO recommendations for diagnosis and classification of diabetes mellitus or similar. Where multiple measures are used, cumulative incidence will be analysed preferentially.

2. Coeliac disease – defined by characteristic histological features (intraepithelial lymphocytes, crypt hyperplasia and villous atrophy) with improvement in symptoms and histology after institution of a gluten free diet, a medical diagnosis, or a surrogate marker such as IgA tissue transglutaminase or IgA endomysial antibodies.
Primary assessment: medical diagnosis of coeliac disease using a histological diagnosis.

Where multiple measures are used, cumulative incidence will be analysed preferentially.

3. Inflammatory bowel disease (Crohn's disease or Ulcerative colitis) – defined as a medical diagnosis.

Primary assessment: medical diagnosis using a histological diagnosis. Where multiple measures are used, cumulative incidence will be analysed preferentially.

4. Autoimmune thyroid disease (Graves' disease or Hashimoto's thyroiditis) - defined as a medical diagnosis.

Primary assessment: medical diagnosis using serology and thyroid function testing. Where multiple measures are used, cumulative incidence will be analysed preferentially.

5. Juvenile rheumatoid arthritis – defined as a medical diagnosis.

Primary assessment: medical diagnosis using the 2001 revised International League of Associations for Rheumatology (ILAR) classification criteria. Where different time-points are reported, then the cumulative incidence to the latest reported time-point will be used preferentially. Where multiple measures are used, cumulative incidence will be analysed preferentially.

6. Vitiligo - defined as a medical diagnosis.

Primary assessment: medical diagnosis using the Vitiligo European Task Force 2007 criteria or similar. Where multiple measures are used, cumulative incidence will be analysed preferentially.

7. Psoriasis - defined as a medical diagnosis.

Primary assessment: medical diagnosis. Where multiple measures are used, cumulative incidence will be analysed preferentially.
Study selection and Data Extraction

Study selection

Two members of the research team (RB and VGL) will independently review titles and abstracts of identified studies. The full text of the paper will also be independently assessed by RB and VGL, and will be assessed for eligibility against the inclusion criteria. Any discrepancies will be resolved through discussions with the research team and, as appropriate, the study sponsor (UK Food Standards Agency, FSA). Electronic records will be kept regarding included and excluded studies for audit purposes, specifying reasons for any exclusion, and these details will be included in the final report. Full text articles will be reviewed in duplicate (by two research team members - RB and VGL), and studies for inclusion will be selected – any discrepancies will be resolved through discussions with the research team and the FSA, as appropriate. The reasons for the exclusion of any relevant studies will be recorded, however ineligible studies will not be analysed further.

Data extraction

A pilot of the data extraction form will be undertaken using a minimum of 5 papers, after which the extraction form will be amended/updated as necessary. The data extraction form will be used to extract the relevant data fields from each included study independently (by two research team members - RB and VGL), and where appropriate data will be entered into Stata IC 12 statistical software for meta-analysis.
Risk of bias (quality) assessment

Review level bias

Publication bias will be assessed using funnel plots and Egger's test. Where asymmetry is evident on the funnel plot, a trim and fill analysis will be used. Possible causes for asymmetry other than publication bias (e.g., between study heterogeneity) will also be considered. Where significant population-based cohorts or randomised controlled trials have assessed mode of infant feeding but not reported relevant atopic or autoimmune outcomes, we will consider contacting authors for original datasets if atopic or autoimmune outcome assessments appear to have been made.

Study level bias

The risk of bias in included RCTs will be assessed using the Cochrane Collaboration Risk of bias tool, which includes sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting, and other bias. RCTs will be considered at low risk of bias where the risk of bias is judged to be low for all key domains of the Cochrane Risk of bias tool. The risk of bias in included cohort and case control studies will be assessed using the National Institute for Clinical Excellence methodological checklist for cohort and case-control studies respectively, which includes considerations of subject selection, assessment of exposure and outcome, and measures to assess confounding. Studies will be considered at low risk of bias where most of the criteria in the checklist are addressed, and those that are not addressed or not reported are judged unlikely to change the study findings. For both RCTs and cohort studies, a level of <20% loss to follow up for atopic/autoimmune outcomes will generally be accepted as representing low risk of bias from incomplete outcome data, if there are no other features to suggest increased risk of bias. For all studies, a
A summary Table of Study Characteristics will be presented for each relevant exposure and outcome, which will include a summary of each study's risk of bias, in addition to the population characteristics, methods used for assessing exposure and for outcome assessment.

**Strategy for data synthesis**

Where appropriate, meta-analysis will be undertaken. If meta-analysis is deemed inappropriate, individual study results will be summarised and a balanced conclusion made.

Separate analyses will be undertaken for each disease outcome, for each group of similar outcome assessment methods for any given disease, and for each intervention/exposure.

Results for randomised or quasi-randomised controlled trials, prospective cohort or longitudinal studies, or where appropriate retrospective cohort studies, nested case-control studies or other case-control studies will be reported separately for each comparison.

**Data extraction**

Data will be extracted either using raw values, 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 will be used in preference, where available.

Random effect meta-analyses will be performed to allow for the anticipated heterogeneity between the studies.

**Heterogeneity**

Heterogeneity will be quantified using $I^2$. We will explore reasons for heterogeneity using subgroup analyses based on study level factors. Where extreme levels of heterogeneity are detected ($I^2 > 75\%$), we will perform sensitivity analyses to assess the effect of excluding outliers, and re-consider whether quantitative data synthesis is appropriate. Where possible, meta-regression and subgroup analysis will be used to explore sources of heterogeneity arising from study characteristics - ordered forest plots and graphical methods will be used to
further investigate potential effects of continuous confounders on study effects. Individual patient data analysis will not be undertaken.

Data analysis

Data from individual studies will be pooled using the generic inverse variance method. Pooled results for binary outcomes will be presented as relative risks with 95% confidence intervals and 2-sided p values, and also expressed as risk differences where possible. Pooled results for continuous outcomes measured using similar scales will be presented as mean differences with 95% confidence intervals and 2-sided p values. However, where different scales are pooled across studies, we will report results using standardised mean differences. P<0.05 will be considered statistically significant. Relevant results will be presented in Summary of Findings tables similar to those used by the Cochrane Collaboration ¹⁵. All analyses will be performed using STATA IC 12.

Planned subgroup analyses

1. High study quality - high quality RCT or cohort studies as defined above will be separately analysed.

2. Increased disease risk - studies of populations at increased risk for atopic or autoimmune disease will be separately analysed - for example infants with a family history of atopic or autoimmune disease.

3. Type of data - unadjusted versus adjusted data. Factors that we expect to be adjusted for within studies: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma outcomes); maternal age; maternal education or socioeconomic status; mode of delivery.
4. Clear definition of breastfeeding status - studies which used definitions of exclusive/predominant breastfeeding which conform to WHO definitions will be analysed separately.

5. Exclusive breastfeeding - where data are available, we will separately analyse outcomes for duration of exclusive breastfeeding and duration of predominant breastfeeding, as defined by WHO.

Graphical exploration of heterogeneity

1. Study year (average year of assessment/birth for study population)
2. Average age of study population at examination/assessment

Review registration

This systematic review will be registered with the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/Prospero), prior to selecting any studies from the search results. This review protocol has been revised following peer review by the UK Food Standards Agency, the UK Scientific Advisory Committee on Nutrition, independent experts Professor Graham Devereux and Dr Carina Venter, and the Lancet.

Dissemination of findings

The findings of this review will inform the Food Standards Agency review of infant feeding which will in turn inform the revised Department of Health guidance on infant feeding in the UK. The reviews will be submitted for publication as peer reviewed manuscripts in academic journals, and presented at national and international conferences. A summary of the findings
will be sent to relevant stakeholders such as charities, health and educational institutions involved in advising on or supporting infant feeding in the UK.

**References**


