EVIDENCE-BASED CHILD HEALTH: A COCHRANE REVIEW JOURNAL
Evid.-Based Child Health **6**: 1322–1339 (2011)
Published online in Wiley Online Library (http://www.evidence-basedchildhealth.com). **DOI:** 10.1002/ebch.827

Overview of Reviews

The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews

Michelle Foisy,[1] Robert J. Boyle,[2,3]* Joanne R. Chalmers,[4] Eric L. Simpson[5] and Hywel C. Williams[6]
[1]*Cochrane Child Health Field, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada*
[2]*Department of Pediatrics, Imperial College London, London, UK*
[3]*National Institute for Health Research Comprehensive Biomedical Research Centre, Imperial College Healthcare NHS Trust, London, UK*
[4]*Centre of Evidence-Based Dermatology, University of Nottingham, Nottingham, UK*
[5]*Department of Dermatology, Oregon Health & Science University, Portland, Oregon, USA*
[6]*Centre of Evidence-Based Dermatology, Nottingham University Hospitals NHS Trust, Nottingham, UK*

Background: Eczema is the most common inflammatory skin disease of childhood, characterized by an itchy red rash that usually involves the face and skin folds. There is currently no curative treatment for eczema, so the reduction of eczema incidence through disease prevention is a desirable goal. Potential interventions for preventing eczema include exclusive breastfeeding, hydrolysed protein formulas and soy formulas when bottle feeding, maternal antigen avoidance, omega oil supplementation, prebiotics and probiotics.

Objectives: This overview of reviews aims to present the current body of data from Cochrane and non-Cochrane reviews to provide the most up-to-date evidence on the efficacy and safety of interventions to prevent eczema in infants and children at different risk levels for developing allergic disease.

Methods: Our pool of Cochrane and non-Cochrane reviews came from the 2010 United Kingdom *National Health Service* (*NHS*) *Evidence Skin Disorders* Annual Evidence Updates Mapping Exercise on Atopic Eczema. This group used a comprehensive search strategy last conducted in August 2010 to identify all systematic reviews on eczema prevention. We identified all reviews that met our pre-specified inclusion criteria, and data were extracted, analysed, compiled into tables and synthesized using quantitative and qualitative methods.

Main results: Seven systematic reviews containing 39 relevant trials with 11 897 participants were included in this overview. Overall, there was no clear evidence that any of the main interventions reviewed reduced eczema incidence. In subgroup analyses of infants at high risk of allergic disease, an observational study found that exclusive breastfeeding for at least six months compared with introduction of solids at three to six months decreased the incidence of eczema by 60% (risk ratio (RR): 0.40; 95% confidence interval (CI): 0.21, 0.78), and a randomized controlled trial found that prebiotics compared with no prebiotics decreased incidence by 58% (RR: 0.42; 95% CI: 0.21, 0.84). However, each of these findings was based on the results of a single small trial, and no intervention reduced eczema incidence beyond the first two years of life. Although we pre-specified incidence of atopic eczema (i.e. eczema associated with immunoglobulin E (IgE) sensitization) as a primary outcome, data on whether participants diagnosed with eczema were truly atopic were largely lacking from systematic reviews. Similarly, data on atopy, measured using skin prick tests or specific IgE tests to allergens, were not reported in many reviews. No interventions were found to decrease atopy when reported. Adverse events data were generally lacking, but data from a trial of probiotics versus no probiotics showed significantly more spitting up in the first one (RR: 1.88; 95% CI: 1.03, 3.45) and two (RR: 1.69; 95% CI: 1.02, 2.80) months of life, but no overall increase in risk of gastrointestinal symptoms in the first year.

Authors' conclusions: Although there is currently no clear evidence showing that any of the interventions examined in this overview prevent eczema in participants not selected for risk of allergic disease, there is some evidence that exclusive breastfeeding for at least six months and prebiotics might reduce eczema incidence in high-risk participants. However, these conclusions are based on limited evidence with methodological shortcomings. Future research on prevention of eczema is needed and should examine different types of hydrolysed formulas, prebiotics and probiotics, as well as enhancement of the skin barrier and other novel approaches in infants at different risk levels for developing allergic disease.

Keywords: eczema, overview, skin disease, systematic review

Plain Language Summary

Eczema is a common skin disease that affects 5–20% of babies and children. It is a condition that typically

*Correspondence to: Dr Robert J. Boyle, Department of Pediatrics, Imperial College London, Wright Fleming Building, Norfolk Place, London W2 1 PG, UK. E-mail: r.boyle@imperial.ac.uk.

comes and goes for years. The skin of people with eczema becomes dry, red, sore and very itchy. Currently, there are no treatments that can make eczema go away for good, so trying to prevent your child from getting eczema in the first place seems like a good idea. We were disappointed not to find any clear evidence that the things tried so far actually do prevent eczema. It seems like exclusive breastfeeding for at least six months or, if this is not possible, supplements that encourage friendly gut bacteria (called prebiotics) might help prevent eczema in infants born into families who already have eczema, asthma or hay fever, but at the moment this is only a suggestion based on a couple of small studies. Much bigger and better studies are needed to see whether these results are true and whether eczema can be prevented.

Background

Description of the condition

Eczema is a chronic inflammatory skin disease characterized by an itchy red rash. It is the most common inflammatory skin disease of childhood, affecting 5–20% of children at any one time (1–3). The disease is characterized by intractable itching and erythema, with associated surface changes such as scaling, thickening (lichenification), excoriations, papules, vesicles and oozing. Although eczema can affect any part of the body, in children it commonly affects the cheeks, neck and skin folds of the knees and elbows. Children with eczema carry an increased risk for secondary skin infections, and the disease is often associated with IgE-mediated diseases such as asthma, food allergy and allergic rhinitis (4). The one-year period prevalence of eczema symptoms varies from 20% in Northern Europe and the US to 5% in the southeastern Mediterranean (1). Only 2% of children with eczema under the age of five years have severe disease, and 84% have mild disease (5).

There is wide variation in the prevalence of eczema between different countries. Data from the International Study of Asthma and Allergies in Childhood in over 100 countries worldwide show that the prevalence of eczema and severe eczema symptoms is increasing in six- and seven-year-old children in developed and developing countries, for reasons which are still unclear (6). While genetic factors, including those which code for skin barrier proteins such as filaggrin are important (7), genetics alone cannot explain the increase in eczema prevalence or its increased prevalence in migrants and people with a higher socioeconomic status (8). The specific environmental exposures that explain eczema risk are still unknown, but early microbial exposure (9) and variations in exposure to urban environments may play a role (10–12).

The severity of eczema is variable, ranging from localized mild scaling to generalized involvement of the whole body with redness, oozing and frequent secondary bacterial infection. The dominant symptom is intractable itching, which can induce a vicious cycle of scratching that leads to skin damage and more itching – the so-called "itch scratch itch" cycle. The itch of eczema can be triggered by sweating and rough clothing such as wool. There is also a tendency to generally dry skin which is worsened by low humidity, cold weather and use of soaps. Eczema usually starts within the first six months of life, and by one year, 60% of those likely to develop the disease will have done so (13). Therefore, primary prevention strategies need to be implemented in the prenatal and/or early postnatal period. In 60–70% of children remission occurs by the age of 15, although some children relapse later. In the more severely affected child, development and puberty may be delayed (14).

In children, the social and emotional impact of eczema can be greater than that of other chronic diseases such as type I diabetes (15). The itching can adversely affect quality of life through chronic sleep disturbance, and the disease can be associated with complications such as bacterial and viral infections (16). The unsightly appearance of the skin and the need to apply greasy ointments can limit a child's inclination to participate in social and sporting activities and thus affect their confidence. Children and teenagers with eczema often have low self-esteem and relationships can be difficult to initiate and sustain. In 1999, the cost of childhood eczema to the Australian community was estimated at AU $316.7 million/year (US $239.3 million; Euro 195.9 million) (17). The healthcare costs of eczema in children and adults are comparable to those of epilepsy, emphysema and other chronic diseases (18–21). Direct costs to the family are encountered when purchasing treatments, special clothing and bedding; indirect costs are experienced from lost working days when parents are looking after a sick child. The wider economic implications lie in the costs of health professionals, the lost opportunities of parents of sick children and the child who, as a result of missed schooling, has limited employment prospects. Eczema often coexists with asthma, food allergy and/or allergic rhinoconjunctivitis, and genes associated with eczema are also associated with other allergic diseases; this suggests a common pathogenesis, and it is therefore possible that eczema prevention may impact on the risk of allergic sensitization or non-eczematous allergic diseases. Although there are several effective treatments for the symptoms and appearance of eczema, there is currently no curative treatment, so prevention of eczema is an important goal in trying to reduce the burden of disease in the community.

The World Allergy Organization divides eczema into 'atopic eczema' and 'non-atopic eczema' according to the presence or absence of IgE sensitization to common environmental allergens such as pollen, house dust mite, milk or egg (22). While the majority of children with eczema seen in hospitals in developed countries are atopic, up to 40% of children with

DOI: 10.1002/ebch.827

eczema in the community have non-atopic eczema, and this percentage can rise to 100% in some developing countries (23,24). The presence or absence of atopy does not help our clinical ability to diagnose eczema (25), whereas it may correlate with eczema severity and severe disruption of the skin barrier. The term 'atopic eczema' or 'atopic dermatitis' is frequently used loosely in published trials and reviews to denote the clinical phenotype of eczema even in the absence of demonstrable IgE antibodies. Throughout this overview, we use the preferred World Allergy Organization term 'eczema' to refer to the clinical phenotype, and 'atopic eczema' when atopy has been established (22). This overview will review strategies for preventing eczema in infants (defined as those aged zero to two years) and children (aged between two and 18 years).

Description of the interventions

Several interventions to prevent eczema have been proposed and tested, primarily based on allergen avoidance, but despite this, there are no clear, evidence-based guidelines for eczema prevention (26). This overview examines evidence for seven interventions for preventing eczema: (1) promotion of exclusive breastfeeding for a defined period of time, (2) hydrolysed protein formulas for infants who are not exclusively breastfed, (3) soy formulas for infants who are not exclusively breastfed, (4) maternal dietary antigen avoidance, (5) omega-3 or -6 fatty acid supplementation, (6) prebiotics and (7) probiotics. These strategies have been tested in infants and children, sometimes in subgroups who are at high risk of developing eczema as determined by family history of allergic disease, with the aim of reducing eczema prevalence in the short and long term. We also wished to explore whether breastfeeding *per se* and maternal avoidance of nondietary allergens such as pet fur or house dust mite could reduce eczema incidence, but we failed to find suitable reviews that met our inclusion criteria in these important topic areas.

How the interventions might work

Formula-based interventions and allergen avoidance are derived from the known association between eczema and IgE sensitization, although the temporal, directional and causal relationships between eczema and IgE sensitization have not been established (23,27). Dietary allergen avoidance features heavily in the early literature because of the close association between eczema and food allergy (28). More recent observations suggest that early exposure to common dietary allergens may actually be protective against food allergy, by promoting the development of immune tolerance before allergic sensitization through other routes can occur (29). However, it is unclear how this might relate to eczema prevention, as some data suggest that eczema and disturbed skin barrier function may predispose to food allergy development rather than food allergy leading to eczema development (30,31).

To date, interventions to modify the infant's exposure to dietary antigens pre- or postnatally have been the major focus of eczema prevention research, on the basis that these might prevent food sensitization and thereby promote intestinal and skin health. Such interventions include the promotion of *exclusive breastfeeding* for a defined period of time, *maternal dietary antigen avoidance* and the use of *hydrolysed protein formula* (in which the allergenic properties of cow's milk are reduced by breaking down the proteins in the milk) or *soy formula* for those infants who are not exclusively breastfed.

More recent studies have attempted to capitalize on the theoretical link between eczema and intestinal health, such as differences in intestinal microbiota composition in eczema and possible altered intestinal permeability and inflammatory markers in people with eczema (32,33). The presence of an altered intestinal milieu in infants at risk for developing eczema has been shown in many – but not all – studies, and is therefore an area of ongoing controversy and research (34,35). Dietary interventions such as *prebiotic* and *probiotic supplementation* may modify early intestinal microbiota development (9,33). *Omega fatty acids* have immune effects which may be beneficial for preventing the development of allergic immune responses.

Other approaches for eczema prevention have focused on Th1 or regulatory T-cell type immune responses, which have been found to be altered in eczema (36). The close association between eczema and allergic sensitization (atopy) has also led some investigators to test the effects of avoiding specific aeroallergens such as pet allergens and house dust mites. Promotion of skin barrier function by use of emollients in early life is another approach that has been suggested (37), based on the observations that skin barrier dysfunction may play a role in initiating eczema. In 2006, Palmer *et al*. showed that genetic mutations in the gene encoding the skin barrier protein filaggrin predisposes to the development of eczema (7), a finding that has now been replicated in over 30 studies (38). Several lines of evidence support a skin barrier approach to eczema prevention including data showing that barrier dysfunction precedes inflammation in neonates with a filaggrin gene mutation (39) and early petrolatum ointment use appears to have a protective effect on eczema development (40). It is also possible that protecting the barrier from birth may reduce IgE sensitization and the subsequent development of other allergic disease, and controlled studies are now underway examining this enhancement of skin barrier approach (41).

Why it is important to do this overview

Eczema is the most common inflammatory skin condition of childhood and has a significant impact in terms

DOI: 10.1002/ebch.827

of morbidity and societal costs. Eczema is often associated with other organ-specific allergic diseases such as asthma and allergic rhinitis, which, together, make up the most common chronic diseases of childhood, the most common diseases causing school absenteeism and the most common reason for childhood hospital admission in some countries (42). There is no curative treatment for eczema, so successful prevention of eczema would therefore be an important scientific achievement. Eczema and associated allergic diseases appear to have become more common in many countries over recent decades, suggesting that modifiable environmental risk factors may be involved in pathogenesis. Successful prevention of eczema may therefore be possible, by either modifying the relevant environmental risk factor(s) or compensating for genetic variations which promote eczema development. Despite an increasing number of interventions, clinical trials and systematic reviews, best practice guidelines for preventing eczema vary internationally (43) and there is a need for an overview of Cochrane and non-Cochrane reviews to inform best clinical practice and advise parents and carers.

Objectives

We aim to present the current body of evidence from Cochrane and non-Cochrane reviews to provide the most up-to-date evidence on pharmacologic and non-pharmacologic interventions for preventing eczema in infants (zero to two years) and children (between two and 18 years) at different risk levels of developing the disease.

Methods

Search methods for identification of reviews

Our pool of potentially included Cochrane and non-Cochrane reviews came from the 2010 United Kingdom *NHS Evidence Skin Disorders* Annual Evidence Updates Mapping Exercise on Atopic Eczema. The group used a comprehensive search strategy to identify all systematic reviews on eczema prevention published from 2000 onwards; they searched the Cochrane Database of Systematic Reviews, EMBASE, MEDLINE, PubMed and the *NHS Evidence Skin Disorders* Library. The latest search was conducted in August 2010 and was also conducted in the previous three years. No restrictions were imposed on publication language, age of participants, participant risk level for developing eczema or type of intervention. To be included, reviews had to fulfil The Cochrane Collaboration's definition of a systematic review (i.e. 'reviews of clearly formulated questions that use systemic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies included in the reviews') (44). Thus, our initial pool of potentially included reviews came from a comprehensive database that searched for all available systematic reviews examining all potential interventions for the prevention of eczema. The group identified reviews that examined interventions spanning nine topic areas: maternal dietary exclusions, breastfeeding, formulas, weaning, diet, probiotics, prebiotics, pet avoidance and avoidance of other aeroallergens[1].

Criteria for considering reviews for inclusion

Our inclusion criteria for all Cochrane and non-Cochrane reviews were as follows:

- Reviews must have included participants between zero and 18 years of age only. If reviews contained both adult and paediatric data, we must have been able to extract the paediatric data separately.
- Reviews must have had a search that was conducted no more than five years ago.
- Reviews must have contained randomized controlled trials (RCTs) only. For two topic areas in which RCTs are ethically difficult to conduct – breastfeeding and pet avoidance – we included reviews that contained non-RCTs to collect data covering all relevant aspects of eczema prevention.
- Reviews must have contained at least one piece of quantitative data to enable calculation of a RR and CI.

All Cochrane reviews met the above criteria and were included. For all topic areas that did not have an included Cochrane review, a maximum of one non-Cochrane review on that topic area was included. If two or more non-Cochrane reviews covering the same topic area met the above inclusion criteria, we included the review that was the most up-to-date. Non-Cochrane reviews were excluded if they analysed data from one or more Cochrane reviews that we had already included in this overview.

Types of outcome measures

Our two pre-specified primary outcomes were incidence of eczema (based on the clinical phenotype as diagnosed by trial investigators) and incidence of atopic eczema (based on the presence of IgE sensitization) (22). Our pre-specified secondary outcome measures were atopy/IgE sensitization, eczema severity, time to development of eczema, quality of life and health-care utilization. Even though our search strategy was only designed to identify reviews on eczema prevention, we also pre-specified incidence of asthma/wheezing and incidence of all allergic disease

[1] The Cochrane review on promotion of exclusive breastfeeding (45) was included in two of the NHS Evidence database topic areas ('breastfeeding' and 'weaning'), so we combined both of these topic areas together for the purpose of this overview.

DOI: 10.1002/ebch.827

as secondary outcomes. As the search for reviews on these topics was not comprehensive, we have opted to report these data in an Appendix. When available, data on adverse events were also extracted.

Subgroup analyses

We conducted two pre-specified subgroup analyses. We examined the effects of interventions in infants (defined here as zero to two years) and children (between two and 18 years), as well as in high-risk participants (those with a family history of allergic disease) and participants not selected for risk.

Data collection and analysis

Selection of reviews

For this overview, two reviewers (MF, JRC) independently assessed the eligibility of each potential review based on the inclusion criteria listed above. Both reviewers agreed on the final set of included reviews.

Assessment of methodological quality of included reviews

Two reviewers (ELS, JRC) independently assessed the methodological quality of each included review using the 'Assessment of Multiple Systematic Reviews' (AMSTAR) tool (46). Both reviewers evaluated whether each review satisfied the 11 different criteria of the AMSTAR tool. In addition to recording which AMSTAR criteria were fulfilled, our reviewers also made a subjective assessment of overall quality of each review by assigning each review an overall rating of 'good', 'fair' or 'poor' based on the global evaluation of the review and informed by the AMSTAR criteria. Discrepancies between reviewers were resolved by a third reviewer (MF).

Data extraction and management

One reviewer (MF) extracted the following information from each of the included reviews: inclusion criteria (including population, intervention, comparisons and outcomes), methodological quality of included trials and numeric results. Numeric results were extracted for aggregate data (all ages and risk levels combined) as well as for our pre-specified subgroups examining different ages and risk levels[2]. Numeric results were extracted from the published reviews, and Review Manager 5 (47) was used for all statistical analyses. A second reviewer (JRC) independently verified accuracy of numeric results, and discrepancies were resolved through discussion.

All data contained in the included reviews were dichotomous; therefore, all data in this overview were summarized using RRs with 95% CIs. RRs describe the probability of the event in the treatment group compared with the probability of the event in the control group, and are interpreted as statistically significant if the 95% CIs do not touch unity. Random effects modelling was used for all outcomes to provide the most conservative estimate.

For all pooled effect estimates, the accompanying I^2 values were reported and represent the degree of statistical heterogeneity between the trials. An I^2 value close to zero percent indicates minimal or no heterogeneity of trials, whereas an I^2 value of 50% or greater indicates substantial heterogeneity (48).

Results

Results of the search

The authors of the 2010 United Kingdom *NHS Evidence Skin Disorders* Annual Evidence Updates on Atopic Eczema identified 28 systematic reviews (six Cochrane reviews and 22 non-Cochrane reviews) which covered eczema prevention strategies. The six Cochrane reviews (45,49–53) were included in this overview and covered five topic areas: breastfeeding, formulas (two reviews), maternal dietary exclusions, prebiotics and probiotics. Three topic areas did not have an included Cochrane review (diet, pet avoidance and avoidance of other aeroallergens). One non-Cochrane review on diet (54) satisfied our inclusion criteria and was also included in our overview.

None of the non-Cochrane reviews examining pet avoidance or avoidance of other aeroallergens met our inclusion criteria, although we did attempt to obtain data files from the authors of one review on pet avoidance (55) so that we could calculate RRs and CIs and therefore include the review in our overview. We were, however, unable to obtain the necessary data, and the review was excluded. We also attempted to obtain data files from the authors of a review on breastfeeding compared with no breastfeeding (56), because our included Cochrane review only assessed the effect of prolonged exclusive breastfeeding compared with the introduction of complementary solid or liquid foods following a short period of exclusive breastfeeding, and did not address the question of whether to breastfeed at all. We were unsuccessful in obtaining the data file that would allow for calculation of RRs and CIs, and this review was also excluded.

Description of included reviews

In total, seven systematic reviews were included in this overview (45,49–54). Each review examined a different intervention: maternal dietary antigen avoidance (Anti), exclusive breastfeeding for a defined period of time (Breast), omega-3 and -6 fatty acid supplementation (Omega), hydrolysed protein formula (Protein), prebiotics (Pre), probiotics (Pro) and soy formula (Soy). Table 1 presents the characteristics of the included reviews.

[2] Where trials or reviews documented outcomes for the same patients at both infancy and childhood, we chose to include only the childhood data in the aggregate data.

DOI: 10.1002/ebch.827

Table I. Characteristics of included Cochrane and non-Cochrane reviews

Review topic Type of review	Review title Authors Last assessed as up-to-date	Number of studies Pooled sample size (range)	Population	Intervention	Comparison	Outcomes for which data are reported
Breastfeeding Cochrane review	Optimal duration of exclusive breastfeeding Kramer MS, Kakuma R 2006	22 10 168 (26–3483)	Lactating mothers and their healthy, term, singleton infants	Exclusive breastfeeding for at least three months	Continued exclusive breastfeeding or mixed breastfeeding (other liquid or solid foods)	Child outcomes: growth, infections, morbidity, mortality, micronutrient status, neuromotor and cognitive development, asthma, atopic eczema, other allergic diseases, diabetes, blood pressure and subsequent chronic diseases Maternal outcomes: postpartum weight loss, duration of lactational amenorrhoea and chronic diseases
Diet non-Cochrane review	Omega-3 and -6 oils for primary prevention of allergic disease: systematic review and meta-analysis Anandan C, Nurmatov U, Sheikh A 2008	6 1337 (65–516)	Pregnant or lactating women and/or infants without an existing allergic condition, at high and low risk of developing eczema/atopic dermatitis, allergic rhinitis, asthma and/or other allergic disorders	Omega-3 and omega-6 fatty acid supplementation either alone or in combination	Placebo	Eczema/atopic dermatitis, asthma, allergic rhinitis, food allergy, skin prick tests, total IgE levels, disease severity, lung function, neonatal cytokines, plasma fatty acids
Formulas Cochrane review	Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants Osborn DA, Sinn JKH 2006	18 7680 (16–5317)	Infants in the first six months of life without clinical evidence of allergy	Early short- term hydrolysed formula or prolonged use of a hydrolysed formula (any type)	Human milk or cow's milk	Primary: all allergic diseases and food intolerance Secondary: asthma, atopic dermatitis/eczema, allergic rhinitis, cow's milk or soy protein allergy or intolerance, food allergy or intolerance, urticaria and anaphylaxis Harms: growth, cost and infant feed refusal
Formulas Cochrane review	Soy formula for prevention of allergy and food intolerance in infants Osborn DA, Sinn JKH 2006	3 772 (50–487)	Infants in the first six months of life without clinical evidence of allergy or food intolerance	Soy formula	Human milk, cow's milk or hydrolysed formula	Primary: all allergic diseases and food intolerance Secondary: growth and cost

DOI: 10.1002/ebch.827

Table I. (*Continued*)

Review topic Type of review	Review title Authors Last assessed as up-to-date	Number of studies Pooled sample size (range)	Population	Intervention	Comparison	Outcomes for which data are reported
Maternal dietary exclusions Cochrane review	Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child Kramer MS, Kakuma R 2006	All studies: 4 Prevention only: 3 All studies: 417 (17–210) Prevention only: 400 (26–210)	Pregnant or lactating women at high risk for giving birth to an atopic child based on history of atopic disease (eczema, asthma or hay fever), and lactating mothers of infants with established atopic eczema	Diet with exclusion or reduced quantity of potentially antigenic foods (cow milk, egg, peanuts, fish and chocolate)	Standard diet	Primary: occurrence and severity of atopic disease in the child Secondary: nutritional status of the mother and foetus, other pregnancy outcomes, positive skin prick test to ingested antigens and cord blood IgE levels
Prebiotics Cochrane review	Prebiotics in infants for prevention of allergic disease and food hypersensitivity Osborn DA, Sinn JKH 2007	7 837 (30–259)	Infants in the first six months of life without clinical evidence of allergic disease or food hypersensitivity, with and without risk factors for allergic disease and food hypersensitivity	Any prebiotics added to human milk or infant formula	Control (placebo or no treatment) or a different prebiotic	Primary: all allergic diseases and food hypersensitivity Secondary: asthma, dermatitis/eczema, allergic rhinitis, cow's milk or soy protein hypersensitivity or allergy, food allergy, urticaria and anaphylaxis Harms: growth, costs, infant feed refusal and infection
Probiotics Cochrane review	Probiotics in infants for prevention of allergic disease and food hypersensitivity Osborn DA, Sinn JKH 2007	12 2974 (62–1223)	Enterally fed infants in the first six months of life without clinical evidence of allergic disease or food hypersensitivity, with and without risk factors for allergy and food hypersensitivity	Any probiotics added to human milk or infant formula, with or without added prebiotics	Control (placebo or no treatment) or a different probiotic	Primary: all allergic diseases and food hypersensitivity Secondary: asthma, dermatitis/eczema, allergic rhinitis, cow's milk or soy protein hypersensitivity or allergy, food allergy, urticaria and anaphylaxis Harms: growth, cost, infant feed refusal and infection with probiotic bacteria

DOI: 10.1002/ebch.827

All included reviews were published between 2006 and 2009, and the searches for primary trials included in those reviews were conducted between 2006 and 2008. In total, the included reviews contained 72 trials and 24 185 participants; however, not all trials included in the reviews were included in this overview: many trials did not report on outcomes relevant to this overview and one trial examined the treatment, but not prevention, of eczema. Therefore, in this overview, there are a total of 39 included trials containing 11 897 participants. Ninety-two percent of trials included in this overview were RCTs, and all but one review (Breast) contained only RCTs.

Search methods

All seven reviews searched CENTRAL and MEDLINE, and all but one (Anti) searched EMBASE and reference lists. Five reviews (Breast, Pre, Pro, Protein, Soy) searched CINAHL and looked for published abstracts, another five (Anti, Pre, Pro, Protein, Soy) searched conference proceedings, three (Anti, Breast, Omega) contacted experts and/or authors and two reviews (Anti, Protein) hand searched journals.

Participants

The types of participants included in this overview varied between reviews. In three reviews (Pre, Protein, Soy), the interventions were given to infants in the first six months of life without clinical evidence of allergy, both with and without risk factors for development of allergic disease. In two reviews (Anti, Breast), the interventions were given to pregnant or lactating women, and outcomes were measured in the infants. In the last two reviews (Omega, Pro), the intervention was given to pregnant or lactating women and/or infants with or without clinical evidence of allergy.

Of the seven included reviews, six included participants at varying risk levels for developing allergic disease, and one included only high-risk participants (Anti). The review authors defined risk level in similar ways. Five reviews (Anti, Pre, Pro, Protein, Soy) defined 'high-risk' participants as those with a family history of atopic or allergic disease in a first-degree relative and/or high cord blood IgE, whereas participants 'not selected for risk' were defined as healthy participants with no family history of allergy in a first-degree relative and/or participants not selected on the basis of heredity. Two reviews did not define 'high-risk' participants and those 'not selected for risk', but provided the information necessary for us to determine which category the participants belonged to, based on the above definitions.

Interventions

One review (Omega) compared an active treatment to placebo, six reviews (Anti, Breast, Pre, Pro, Protein, Soy) compared an active treatment to a control intervention and two reviews (Pre, Protein) compared an active treatment to another active treatment. Some reviews examined more than one type of comparison.

Outcome measures

All seven reviews pre-specified outcome measures, which were homogenous across reviews. All reviews searched for data on all allergic disease, including eczema, atopic eczema, asthma, rhinitis and food hypersensitivity or allergy. 'Atopy' was not pre-specified as an *a priori* outcome in many of the reviews, although it was recorded in many of their included trials. Timing of measurements for all outcomes varied across reviews.

Even though five reviews (Anti, Breast, Pre, Pro, Protein) searched for data on atopic eczema, only two (Pre, Pro) used the World Allergy Organization's definition of atopic eczema, defined as demonstration of an IgE response using either skin testing or serological testing (22). Data on atopic eczema presented in these two reviews have been reported in this overview under the heading of 'atopic eczema', whereas data in the other three reviews (Anti, Breast, Protein) have been presented in this overview under the general heading of 'eczema'.

All reviews but one (Pre) presented data on asthma and/or wheezing. From this point onwards, both of these diagnoses will be referred to as data on 'asthma'.

Data analysis

All included reviews conducted at least one meta-analysis. In one review (Pro), we identified two errors in the meta-analyses and therefore re-analysed the relevant outcomes using original data from the affected trials. The errors noted were as follows: (1) inclusion of data from the same trial subjects twice in the same meta-analysis (analysis 1.5); and (2) inclusion of a trial in the 'atopic eczema' meta-analysis (1.6) which should have been included in the 'eczema' meta-analysis (1.5), as the data referred to all eczema rather than IgE-associated eczema as defined by the World Allergy Organization (22).

Methodological quality of included reviews

Based on our AMSTAR assessments, all included reviews were rated as 'good quality' on our 'good, fair, poor' scale. However, there were minor methodological limitations in the included reviews. Six reviews (Anti, Breast, Pre, Pro, Protein, Soy) did not assess publication bias, and it was unclear whether two reviews (Anti, Breast) carried out duplicate study selection and/or data extraction. One review (Omega) did not provide details of excluded studies. All seven reviews were otherwise methodologically sound.

Methodological quality of included trials

All six Cochrane reviews (Anti, Breast, Pre, Pro, Protein, Soy) used various aspects of the Cochrane

DOI: 10.1002/ebch.827

Table II. Eczema (all ages and risk levels)

Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	3731 (2)	0.75 (0.42, 1.32)	61
Hydrolysed formula versus cow's milk formula (prolonged feeding)	1478 (8)	0.87 (0.70, 1.08)	0
Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	912 (3)	0.84 (0.58, 1.23)	19
Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	823 (7)	0.92 (0.72, 1.17)	0
Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	1061 (4)	0.88 (0.73, 1.05)	0
Hydrolysed formula versus human milk (early short-term feeding)	90 (1)	0.48 (0.05, 4.41)	—
Hydrolysed formula versus cow's milk formula (early short-term feeding)	77 (1)	0.34 (0.04, 3.15)	—
Soy formula versus cow's milk formula	744 (3)	1.23 (0.99, 1.53)	0
Maternal antigen avoidance versus standard diet	360 (3)	0.95 (0.63, 1.44)	21
Omega-3 fatty acid supplementation versus placebo	664 (3)	1.10 (0.78, 1.54)	45
Omega-6 fatty acid supplementation versus placebo	259 (2)	0.80 (0.56, 1.16)	0
Prebiotic versus no prebiotic	432 (2)	0.79 (0.21, 2.94)	80
Prebiotic versus other prebiotic*	**150 (1)**	**0.22 (0.07, 0.76)**[a]	—
Probiotic versus no probiotic†	1492 (6)	0.85 (0.66, 1.08)	46

[a] Significantly favours prebiotic (polydextrose, galacto-oligosaccharide and lactulose).
* Polydextrose, galacto-oligosaccharide and lactulose versus polydextrose and galacto-oligosaccharide;
† This review also reported data on a subgroup of participants with atopic eczema; 1354 participants in four trials contributed to this outcome, and the effect estimate was not significant (RR: 0.85; 95% CI: 0.51, 1.42; I^2: 65%).
Bold text indicates statistical significance.

Risk of Bias tool (48) to evaluate the methodological quality of their included trials. The methodological quality of the trials included in this overview is described below.

The six Cochrane reviews assessed adequacy of randomization, and in the combined 33 included trials, randomization was judged as adequate in 39% of trials, unclear in 46% and inadequate in 15%. The same six reviews also assessed the quality of allocation concealment to treatment groups and judged allocation concealment as adequate in 52% of trials, unclear in 33% and inadequate in 15%. Five of the six reviews containing 30 included trials (Breast, Pre, Pro, Protein, Soy) evaluated incomplete outcome data, which was judged as adequate in 33% of trials, unclear in 7% and inadequate in 60%. Lastly, five reviews containing 30 trials (Anti, Pre, Pro, Protein, Soy) assessed blinding of parents or carers and assessors to interventions[3]. Blinding of parents or carers was judged as adequate in 43% of trials, unclear in 17% and inadequate in 40%, and blinding of assessors was judged as adequate in 53.3% of trials, unclear in 33.3% and inadequate in 13.3%.

The non-Cochrane review (Omega) used two different tools to assess methodological quality of trials. A modified Cochrane Risk of Bias tool was used to assess trials based on five dimensions, and overall trial quality was scored as having a low, moderate or high risk of bias (57). Trials were also scored using the five-point Jadad scale that assessed randomization technique, double-blinding procedure and documentation of losses and withdrawals (58). Five of the six trials were judged as having a low risk of bias and received Jadad scores of 5/5, and the sixth trial was judged as having a moderate risk of bias and received a Jadad score of 3/5.

Effect of interventions

Eczema

Table 2 presents data on overall incidence of eczema in all ages and risk levels combined, and Tables 3 and 4 present subgroup analyses examining incidence of eczema in different ages and risk levels. Data were available for 14 different comparisons.

Exclusive breastfeeding for at least six months compared to introduction of solids at three to six months[4] did not significantly decrease the overall incidence of eczema, based on two trials containing 3731 participants. However, in a subgroup analysis of high-risk infants, exclusive breastfeeding for six months significantly decreased the risk of developing eczema by 60% (RR: 0.40; 95% CI: 0.21, 0.78), an effect that was not significant beyond two years of age or in infants not selected for risk of developing allergic disease.

Compared to cow's milk formula, there was no clear benefit of prolonged feeding of hydrolysed formula (all types) or subgroup analyses of partially or extensively hydrolysed formulas. Prolonged feeding with extensively versus partially hydrolysed formula showed no significant difference. Early short-term feeding of hydrolysed formula (all types) showed no benefit over human milk or cow's milk formula. Soy formula versus cow's milk formula also showed no significant benefit. Maternal antigen avoidance was no better than standard diet, omega-3 or -6 fatty acid supplementation was no better than placebo, and there was also

[3] The sixth review (45) did assess blinding, however, assessments are not reported in this overview because the researchers assessed blinding of their primary outcomes – growth and height – which are not included in this overview.

[4] 'Introduction of solids at three to six months' refers to introduction of nonbreast milk liquids and/or solid food.

DOI: 10.1002/ebch.827

Table III. Eczema subgroup analyses: infants (zero to two years)

Risk level	Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
High risk	**Exclusive breastfeeding for at least six months versus introduction of solids at three to six months**	**135 (1)**	**0.40 (0.21, 0.78)**[a]	—
	Hydrolysed formula versus cow's milk formula (prolonged feeding)	2558 (8)	0.86 (0.70, 1.06)	0
	Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	1726 (3)	0.83 (0.58, 1.21)	19
	Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	1361 (7)	0.90 (0.71, 1.15)	0
	Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	1865 (4)	0.89 (0.74, 1.07)	0
	Soy formula versus cow's milk formula	461 (1)	1.20 (0.95, 1.52)	—
	Maternal antigen avoidance versus standard diet	360 (3)	0.95 (0.63, 1.44)	21
	Omega-3 fatty acid supplementation versus placebo	83 (1)	1.49 (0.84, 2.63)	—
	Omega-6 fatty acid supplementation versus placebo	259 (2)	0.80 (0.56, 1.16)	0
	Prebiotic versus no prebiotic	**206 (1)**	**0.42 (0.21, 0.84)**[b]	—
	Probiotic versus no probiotic	1420 (4)	0.86 (0.66, 1.12)	58
Not selected for risk	Exclusive versus mixed breastfeeding for three to seven months	3483 (1)	1.00 (0.60, 1.69)	—
	Prebiotic versus no prebiotic	226 (1)	1.62 (0.62, 4.26)	—
	Prebiotic versus other prebiotic*	**150 (1)**	**0.22 (0.07, 0.76)**[c]	—
	Probiotic versus no probiotic	72 (1)	0.63 (0.21, 1.89)	—

[a] Significantly favours exclusive breastfeeding for three to seven months;
[b] Significantly favours prebiotic;
[c] Significantly favours prebiotic (polydextrose, galacto-oligosaccharide and lactulose).
* Polydextrose, galacto-oligosaccharide and lactulose versus polydextrose and galacto-oligosaccharide.
Bold text indicates statistical significance.

Table IV. Eczema subgroup analyses: children (between two and 18 years)

Risk level	Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
High risk	Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	113 (1)	0.97 (0.50, 1.89)	—
	Hydrolysed formula versus cow's milk formula (prolonged feeding)	950 (2)	0.74 (0.40, 1.38)	40
	Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	651 (1)	0.86 (0.63, 1.17)	—
	Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	510 (2)	0.75 (0.37, 1.51)	46
	Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	661 (1)	0.92 (0.67, 1.26)	—
	Soy formula versus cow's milk formula	283 (2)	1.51 (0.74, 3.10)	18
	Omega-3 fatty acid supplementation versus placebo	516 (1)	0.85 (0.62, 1.18)	—
Not selected for risk	Hydrolysed formula versus human milk (early short-term feeding)	90 (1)	0.48 (0.05, 4.41)	—
	Hydrolysed formula versus cow's milk formula (early short-term feeding)	77 (1)	0.34 (0.04, 3.15)	—
	Omega-3 fatty acid supplementation versus placebo	65 (1)	1.24 (0.79, 1.95)	—

no effect of probiotics compared with no probiotics. None of the above subgroup analyses were significant based on either age or risk level.

When prebiotics were compared to no prebiotics in infants not selected for risk, there was no overall effect on eczema prevention. However, in high-risk infants, prebiotics compared with no prebiotics were found to significantly decrease the risk of developing eczema by 58% (RR: 0.42; 95% CI: 0.21, 0.84). One trial comparing different types of prebiotics found that a combination of polydextrose, galacto-oligosaccharide and lactulose compared with polydextrose and galacto-oligosaccharide alone significantly decreased the incidence of eczema by 78% in infants not selected for risk of developing allergic disease (RR: 0.22; 95% CI: 0.07, 0.76).

Atopic eczema

Although we pre-specified atopic eczema associated with IgE sensitization as one of our two primary

DOI: 10.1002/ebch.827

Table V. Atopy (all ages and risk levels)

Comparison	Outcome	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	Positive skin prick test (unspecified) at six years	331 (1)	0.99 (0.73, 1.35)	—
Maternal antigen avoidance versus standard diet	Positive skin prick test to egg at two years	335 (2)	0.95 (0.52, 1.74)	0
	Positive skin prick test to milk at two years	335 (2)	0.86 (0.16, 4.59)	13
Omega-3 fatty acid supplementation versus placebo	Positive skin prick test for 'any atopy'*	560 (2)	0.92 (0.76, 1.11)	NR
	Positive skin prick test to house dust mites	560 (2)	1.04 (0.81, 1.34)	NR

NR: not reported.
* 'Any atopy' refers to salmon, peanuts, cow's milk, egg white, egg yolk, tuna, house dust mite, cockroach, cat, Alternaria alternate, rye grass and grass mix.

outcomes, only one comparison – probiotics versus no probiotics – provided data examining this outcome. There was no significant difference in the overall incidence of atopic eczema, and subgroup analyses in high-risk infants and infants not selected for risk were also not significant.

Atopy

Table 5 presents data on atopy, measured using skin prick tests to various allergens. Data were available for three different comparisons – exclusive breastfeeding for at least six months versus introduction of solids at three to six months, maternal dietary antigen avoidance versus standard diet and omega-3 fatty acid supplementation versus placebo – and none of the comparisons was significant.

Adverse events

Table 6 presents data on adverse events. Only data in infants was available, and data are presented for nine different comparisons. The only significant comparison was that of probiotics versus no probiotics. Parents reported that significantly more infants receiving probiotics were spitting up at one and two months of age (RR: 1.88; 95% CI: 1.03, 3.45 and RR: 1.69; 95% CI: 1.02, 2.80); however, premature infants receiving probiotics experienced a 65% reduction in necrotizing enterocolitis and/or death (RR: 0.35; 95% CI: 0.15, 0.83).

Asthma and all allergic disease

The attached Appendix contains data on overall incidence of asthma and overall incidence of all allergic disease in participants of all ages and risk levels combined. It also contains subgroup analyses examining the incidence of asthma and all allergic disease in infants and children at high risk and not selected for risk of allergic disease.

No interventions examined in the trials included in this overview reduced the overall incidence of asthma or the incidence of asthma in infants at high risk or not selected for risk of developing allergic disease. In two trials containing 464 children not selected for risk of allergic disease, omega-3 fatty acid supplementation was found to decrease the risk of developing asthma by 52% (RR: 0.48; 95% CI: 0.25, 0.93).

Although prolonged feeding of hydrolysed formula compared to cow's milk formula failed to show any benefit for preventing eczema, evidence from seven trials containing 1434 participants suggested that it might decrease the overall incidence of all allergic disease by 25% (RR: 0.75; 95% CI: 0.59, 0.95). This beneficial effect was also seen in seven trials containing 2514 high-risk infants (RR: 0.76; 95% CI: 0.61, 0.65). No other interventions reduced the overall incidence of all allergic disease or the incidence of all allergic disease in infants or children at high risk or not selected for risk of developing allergic disease.

Discussion

Summary of main results

We found no clear evidence that any of the seven interventions reviewed here prevents the development of eczema. There was, however, weak evidence that some of the interventions may reduce the risk of developing eczema, which supports the value of further research in those areas.

Eczema prevention

There is no evidence that exclusive breastfeeding for at least six months in place of introduction of solids at three to six months, early short-term feeding in the first days of life with hydrolysed formula, feeding with soy formula in place of cow's milk formula, omega-3 or -6 fatty acid supplementation, or prebiotic or probiotic supplementation reduce the risk of developing eczema. There is evidence from one small study that addition of lactulose to the prebiotics polydextrose and galacto-oligosaccharide in the first four months may reduce the incidence of eczema during the first two years of life; however, it is unknown whether this treatment reduces eczema incidence compared with no treatment.

In subgroup analyses, there was evidence from one trial that in high-risk infants who were formula fed

DOI: 10.1002/ebch.827

Table VI. Adverse events: infants (zero to two years)

Comparison	Adverse event	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2
Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	Death in first 12 months	3483 (1)	2.30 (0.21, 25.37)	—
Hydrolysed formula versus cow's milk formula (prolonged feeding)	Feeding problems	141 (1)	2.18 (0.49, 9.68)	—
	Refusal to drink formula	46 (1)	7.62 (0.43, 133.78)	—
Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	Feeding problems	96 (1)	1.38 (0.24, 7.89)	—
Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	Feeding problems	91 (1)	3.07 (0.65, 14.40)	—
Extensively hydrolysed versus partially hydrolysed formula (prolonged feeding)	Feeding problems	95 (1)	0.45 (0.12, 1.69)	—
Maternal antigen avoidance versus standard diet	Preterm birth	236 (2)	10.06 (0.52, 192.26)	NA
Prebiotic versus no prebiotic	Feed intolerance leading to formula discontinuation	226 (1)	1.81 (0.82, 3.99)	—
Prebiotic versus other prebiotic*	Feed intolerance leading to formula discontinuation	150 (1)	1.73 (0.82, 3.67)	—
Probiotic versus no probiotic	Sepsis	367 (1)	0.63 (0.39, 1.04)	—
	Spitting up at one month of age	**188 (1)**	**1.88 (1.03, 3.45)**[a]	—
	Spitting up at two months of age	**188 (1)**	**1.69 (1.02, 2.80)**[a]	—
	Gastrointestinal problems at one month of age	188 (1)	1.47 (0.63, 3.43)	—
	Gastrointestinal problems at two months of age	188 (1)	0.59 (0.22, 1.55)	—
	Gastrointestinal problems in first 12 months	188 (1)	0.93 (0.54, 1.60)	—
	Necrotizing enterocolitis and/or death	**145 (1)**	**0.35 (0.15, 0.83)**[b]	—

NA: not available.
[a] Significantly favours no probiotic;
[b] Significantly favours probiotic.
* Polydextrose, galacto-oligosaccharide and lactulose versus polydextrose and galacto-oligosaccharide.
Bold text indicates statistical significance.

beginning within two weeks of birth and who ceased all breastfeeding by six weeks, prebiotic supplementation reduces the risk of eczema during early infancy. However, extrapolation from this small study is limited by methodological issues such as high loss to follow-up and lack of intention to treat analysis. There was evidence from one observational study that exclusive breastfeeding for at least six months compared with introduction of solids at three to six months in high-risk infants reduces the risk of eczema during infancy. There was no evidence for any intervention having a significant impact on eczema later in childhood, defined here as the period beyond two years of age.

In summary, the effects of lactulose, as well as the effects of exclusive breastfeeding and prebiotics in certain subgroups, are worthy of further study, but no definitive recommendations can be made at present for preventing development of eczema.

Atopic eczema

Only two systematic reviews classified 'atopic eczema' according to accepted international guidelines, and only one review contained data on atopic eczema. This review found no evidence that probiotics are effective for preventing atopic eczema.

Atopy

We found no evidence from the included reviews that exclusive breastfeeding for at least six months, maternal antigen avoidance or omega-3 fatty acid supplementation reduce the risk of atopic sensitization as measured using skin prick tests or specific IgE testing.

Adverse events

Adverse events were generally under-reported, with only a small number of trials reporting adverse events in addition to eczema-related outcomes. In one trial, supplementation for mothers and infants with the probiotic *Lactobacillus reuteri* increased the risk of infants spitting up at one and two months of age, but had no overall effect on the risk of any gastrointestinal problem in the first 12 months of life. One study found that probiotics reduced the risk of necrotizing enterocolitis and/or death when used to treat premature infants at risk of this condition. This is supported by a separate Cochrane review of probiotic use for prevention of necrotizing enterocolitis (59).

Asthma and all allergic disease

Although asthma and all allergic disease were not the primary focus of this overview, we elected *a priori* to

DOI: 10.1002/ebch.827

include them as secondary outcomes. Our non-eczema findings should be interpreted with caution because it is possible that we failed to include important systematic reviews of interventions for asthma and all allergic disease which did not include eczema as an outcome measure.

Analysis of the asthma data in the eczema reviews found that in subgroup analyses, omega-3 fatty acid supplementation reduced the risk of asthma beyond the first two years of life in children not selected for risk of allergic disease. Other interventions studied (exclusive breastfeeding for at least six months, hydrolysed formula, soy formula, maternal antigen avoidance in pregnancy, omega-3 fatty acid supplementation and probiotics) did not significantly reduce risk of developing asthma.

From the data on all allergic disease included in the eczema reviews, there is evidence that prolonged feeding with hydrolysed cow's milk formula in place of unhydrolysed cow's milk formula can reduce risk of any allergic disease both overall and in high-risk infants who cannot be exclusively breastfed in the first months of life. The other interventions studied (exclusive breastfeeding for at least six months, soy formula, maternal antigen avoidance in pregnancy and probiotics) were not effective in reducing the risk of all allergic disease.

Quality of the evidence

Significant numbers of trials and participants have been included in our overview, allowing for reasonably robust conclusions about the effectiveness or lack of evidence of effectiveness of different interventions. A particular problem in some included reviews was the heterogeneity in the nature of the interventions (e.g. partially versus extensively hydrolysed formulas, and whey versus casein formulas) and population (e.g. early, late and prolonged formula feeding; exclusively breastfed, mixed breastfed or exclusively formula fed; and high or normal risk for allergic disease) which makes it difficult to perform meta-analyses in such populations. Trials of prebiotic and probiotic interventions also suffered from heterogeneity in the interventions, and it should be noted that several probiotic trials have been published since the last systematic review on this subject (60–68), warranting an updated review.

The quality of systematic reviews included in this overview was high: six reviews were Cochrane reviews, and all seven reviews in this overview addressed most of the AMSTAR systematic review quality criteria and received overall ratings of 'good'.

Overall completeness and applicability of evidence

Many of the interventions of interest that we identified prior to conducting this overview were captured in Cochrane and non-Cochrane systematic reviews. Comparisons examining exclusive breastfeeding for at least six months, hydrolysed formulae, omega-3 fatty acids and probiotics contained significant numbers of trials and participants and were thus powered to detect important treatment effects. However, analyses of soy formulas, maternal antigen avoidance and prebiotics included smaller numbers of participants and studies so may have missed important treatment effects on incidence of eczema.

Other areas where more systematic reviews and trials are needed are 'interventions to promote normal immune development' and 'interventions to correct skin barrier dysfunction'. The latter is particularly important in view of the growing body of evidence for abnormalities of skin barrier function in eczema. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis (7), and skin barrier dysfunction can be detected prior to eczema development (39).

There is a need for more complete reporting of adverse events within systematic reviews of interventions for eczema prevention. Also, greater numbers of trials must report the effects of these interventions on eczema prevalence beyond infancy, particularly in normal risk infants.

Limitations

This overview was undertaken using a consensus-based process informed by Cochrane Collaboration expertise in preventing bias, and provides a thorough review of several interventions for eczema prevention. A particular strength of the overview was collaboration with the authors of the 2010 *NHS Evidence Skin Disorders* Annual Evidence Update on Atopic Eczema, which ensured a thorough literature search and access to all published systematic reviews of interventions for preventing eczema. All analyses were defined *a priori*, including the inclusion of reviews of nonrandomized studies for two interventions (breastfeeding and pet avoidance) where RCTs are ethically difficult to perform.

The strength of some conclusions was limited by small numbers of trials or participants included in the relevant reviews, and the analysis of probiotic effects was limited by the recent publication of many relevant trials (60–68) such that they have not yet been incorporated into a Cochrane systematic review. A more recent meta-analysis incorporating many of these trials (69) found that probiotic supplementation significantly reduces risk of developing eczema in infancy (RR: 0.79; 95% CI: 0.67, 0.92).

We were unable to extract data from the published systematic reviews on breastfeeding versus no breastfeeding and pet exposure in a form that could be incorporated in this overview. The systematic review of breastfeeding versus no breastfeeding (56) did find a significant protective effect against eczema [odds ratio (OR): 0.70; 95% CI: 0.50, 0.99]; however, when

DOI: 10.1002/ebch.827

one controversial trial was excluded from the analysis, this comparison became nonsignificant (OR: 0.84; 95% CI: 0.64, 1.09). The review on pet exposure (55) found that, in longitudinal studies, exposure to cats (OR: 0.76; 95% CI: 0.62, 0.92), dogs (OR: 0.68; 95% CI: 0.53, 0.87) or 'any furry pets' (OR: 0.79; 95% CI: 0.74, 0.84) was associated with reduced risk of developing eczema. However, one trial noted that when adjustments were made for avoidance behaviour in participants allergic to pets, the protective effect of cats became nonsignificant.

The definitions of 'eczema' and 'atopic eczema' are the subject of much debate and controversy. We elected to group 'all eczema' together for the purpose of this overview, and identified very few reviews which classified 'atopic eczema' according to the World Allergy Organization recommendations.

It is worth noting that very few of the systematic reviews evaluated atopy/allergic sensitization as an outcome, despite it being reported in many of the included RCTs. While this may be justified because atopy/allergic sensitization is not a widely recognized disease entity, the primary prevention of atopy/allergic sensitization may be associated with prevention of later-onset allergic disease and is therefore worth including in future systematic reviews in this area. Also, we found no available data for four of our prespecified secondary outcomes: eczema severity, time to development of eczema, quality of life and health-care utilization. All appear to be important parameters to measure in future trials and systematic reviews; for example, there is little gain in preventing eczema incidence if the absolute number of severe cases (which disproportionately account for most health-care costs) remains unchanged.

Lastly, while some interventions for prevention of asthma and all allergic disease look promising, these findings must be interpreted with caution. These data should not be regarded as complete because our search strategy was designed only to identify eczema reviews, and we likely failed to include important reviews which do not include eczema as an outcome measure.

Agreements and disagreements with other studies or reviews

The results of this overview are broadly in keeping with those of other published trials and reviews of RCTs, but are in less agreement with reviews and practice guidelines which include 'all allergic disease' or 'allergy' as primary outcomes or which include significant numbers of nonrandomized trials. For example, a recent German taskforce on allergy prevention recommended exclusive breastfeeding for four months or, if not possible, the use of a hydrolysed formula for high-risk infants and general avoidance of pets (70). This difference in results might stem from the German taskforce's inclusion of other allergy outcomes and a large number of nonrandomized studies. However, a recent RCT of hydrolysed formula for preventing allergic disease in high-risk infants supports our conclusion that further research is needed before recommending this intervention to prevent eczema (71).

Authors' Conclusions

Implications for practice

This overview of systematic reviews on eczema prevention has not found any clear evidence that any of the main interventions reviewed can reduce eczema incidence. That does not mean to say that some interventions do not work, as new larger, well-reported trials may indeed show a modest benefit in time. However, the current evidence is simply not strong enough to influence practice recommendations. Some interventions, such as soy instead of cow's milk, are unlikely to show a clinically useful benefit based on the lower 95% CIs and the pooled effect estimates. One might take the view that some of the interventions are unlikely to do much harm, but adverse events were poorly reported in many of the included trials.

It is also worth noting that we have not been able to address some of the most commonly asked questions by parents (such as whether exclusive breastfeeding or owning a pet prevents eczema) because of lack of appropriate data which may partially reflect the ethical difficulties of conducting trials in these areas. Furthermore, some interventions such as 'probiotics' are simply too heterogeneous to lump together – some may work, and some may be completely ineffective. This overview has found that the possible benefit of some interventions (such as exclusive breastfeeding or prebiotics) might only be present in infants born to families at high risk for allergic disease, and that the magnitude of risk reduction is larger than the RRs from unselected populations. Again, caution has to be expressed as these results were based on only one trial each with significant limitations.

Implications for research

With regard to eczema prevention, some interventions, such as omega-3 fatty acid supplementation and soy milk instead of cow's milk, can be abandoned and not researched further. Other interventions such as hydrolysed formula, prebiotics and probiotics show inconclusive results and are worthy of further study. New interventions designed to enhance skin barrier function, such as intensive use of emollients or avoidance of alkaline soaps, should also be explored, and a separate overview of reviews examining interventions for preventing asthma and other allergic diseases is warranted.

Acknowledgements

The authors would like to thank Lorne Becker for his advice on methodological issues related to the preparation of this

DOI: 10.1002/ebch.827

overview and Douglas Grindlay for providing information about the search strategy used for the UK *NHS Evidence Skin Disorders* Annual Evidence Updates on Atopic Eczema.

Contributions of Authors

All authors contributed to this overview. MF and JRC assessed reviews for inclusion, MF extracted data and created results tables, JRC verified data accuracy and JRC and ELS rated the methodological quality of reviews. MF wrote the Methods and Results sections, RJB wrote the Background and Discussion and HCW wrote the Authors' Conclusions section. MF is the primary author of this report. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of Interest

RJB has received research grants and speaker fees from Danone, who research and market prebiotics, probiotics and hydrolysed formulas. No other declarations of interest are noted.

References

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; **124**: 1251–1258.
2. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.
3. Shaw TE, Currie GP, Koudelka C, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2010; **131**: 67–73.
4. Beck LA, Leung DYM. Allergen sensitization through the skin induces systemic allergic responses. *J Allergy Clin Immunol* 2000; **106**: S258–S263.
5. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol* 1998; **139**: 73–76.
6. Williams H, Stewart A, von ME, Cookson W, Anderson HR. Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008; **121**: 947–954.
7. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, *et al*. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–446.
8. Williams HC. Atopic eczema. *BMJ* 1995; **311**: 1241–1242.
9. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsarr M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001; **108**: 516–520.
10. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U, *et al*. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 2008; **177**: 1331–1337.
11. Miyake Y, Tanaka K, Fujiwara H, Mitani Y, Ikemi H, Sasaki S, *et al*. Residential proximity to main roads during pregnancy and the risk of allergic disorders in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2009; **21**: 22–28.
12. Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol* 2010; **162**: 964–973.
13. Williams HC, Wutherrich B. The natural history of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press; 2000; 41–59.
14. Baum WF, Schneyer U, Lantzsch AM, Kloditz E. Delay of growth and development in children with bronchial asthma, atopic dermatitis and allergic rhinitis. *Exp Clin Endocrinol Diabetes* 2002; **110**: 53–59.
15. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997; **76**: 159–162.
16. McHenry PM, Williams HC, Bingham EA. Management of atopic eczema. Joint Workshop of the British Association of Dermatologists and the Research Unit of the Royal College of Physicians of London. *BMJ* 1995; **310**: 843–847.
17. Kemp AS. Atopic eczema: its social and financial costs. *J Paediatr Child Health* 1999; **35**: 229–231.
18. Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR, *et al*. Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol* 2002; **46**: 361–370.
19. Kemp AS. Cost of illness of atopic dermatitis in children: a societal perspective. *Pharmacoeconomics* 2003; **21**: 105–113.
20. Herd RM. The morbidity and cost of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press; 2000; 85–95.
21. Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatr Dermatol* 2008; **25**: 1–6.
22. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, *et al*. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; **113**: 832–836.
23. Flohr C, Weiland SK, Weinmayr G, Bjorksten B, Braback L, Brunekreef B, *et al*. The role of atopic sensitization in flexural eczema: findings from the International Study of Asthma and Allergies in Childhood Phase Two. *J Allergy Clin Immunol* 2008; **121**: 141–147.
24. Bohme M, Svensson A, Kull I, Nordvall SL, Wahlgren CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Derm Venereol* 2001; **81**: 193–197.
25. Hanifen JM. Atopiform dermatitis: do we need another confusing name for atopic dermatitis? *Br J Dermatol* 2002; **147**: 430–432.
26. Thygarajan A, Burks AW. American Academy of Pediatrics recommendations on the effects of early nutritional interventions on the development of atopic disease. *Curr Opin Pediatr* 2008; **20**: 698–702.
27. Lowe AJ, Abrahamson MJ, Hoskingz CS, Carlin JB, Bennett CM, Dharmage SC, *et al*. The temporal sequence of allergic sensitization and onset of infantile eczema. *Clin Exp Allergy* 2007; **37**: 536–542.
28. Hill DJ, Hosking CS, de Benedictis FM, Orange AP, Diepgen TL, Bauchau V, *et al*. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy* 2011; **38**: 161–168.
29. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, *et al*. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010; **126**: 807–813.
30. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, *et al*. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011; **127**: 661–667.
31. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008; **121**: 1331–1336.

DOI: 10.1002/ebch.827

32. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH, *et al*. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *J Allergy Clin Immunol* 2003; **111**: 389–395.
33. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* 2011; **107**: 129–134.
34. Adlerberth I, Strachan DP, Matricardi PM, Ahrne S, Orfei L, Aberg N, *et al*. Gut microbiota and development of atopic eczema in three European birth cohorts. *J Allergy Clin Immunol* 2007; **120**: 343–350.
35. Penders J, Thijs C, van den Brandt PA, Kummeling I, Snijders B, Stelma F, *et al*. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut* 2007; **56**: 661–667.
36. Warner JA, Miles EA, Jones AC, Quint DJ, Colwell BM, Warner JO. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994; **24**: 423–430.
37. Simpson EL, Berry TM, Brown PA, Hanifin JM. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol* 2010; **63**: 587–593.
38. Akiyama M. FLG mutations in ichthyosis vulgaris and atopic eczema: spectrum of mutations and population genetics. *Br J Dermatol* 2010; **162**: 472–477.
39. Flohr C, England K, Radulovic S, McLean WH, Campbel LE, Barker J, *et al*. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163**: 1333–1336.
40. Macharia WM, Anabwani GM, Owili DM. Effects of skin contactants on evolution of atopic dermatitis in children: a case control study. *Trop Doct* 1991; **21**: 104–106.
41. Simpson EL, Chalmers JR, Irvine AD, Cork MJ, McClean WHI, Williams HC. Barrier Enhancement for Eczema Prevention; the BEEP feasibility study. Abstract presented at the International Symposium of Atopic Dermatitis, Munich, Germany, 2010.
42. Australian Institute of Health and Welfare. *Australia's Health 2010*. Canberra: AIHW; 2010.; Report No.: AUS 122.
43. Schafer T, Borowski C, Reese I, Werfel T, Gieler U, German Network on Allergy Prevention. Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP). *Minerva Pediatr* 2008; **60**: 313–325.
44. Waters E, Doyle J, Jackson N, Howes F, Brunton G, Oakley A. Evaluating the effectiveness of public health interventions: the role and activities of the Cochrane Collaboration. *J Epidemiol Community Health* 2006; **60**: 285–289.
45. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2002; **1**: CD003517.
46. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; **7**: 10.
47. *Review Manager (RevMan) [computer program]*. Version 5.0. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*; 2009.
48. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009]. 2009.
49. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2006; **1**: CD000133.
50. Osborn DA, Sinn JKH. Prebiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007; **4**: CD006474.
51. Osborn DA, Sinn JKH. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007; **4**: CD006475.
52. Osborn DA, Sinn JKH. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006; **4**: CD003664.
53. Osborn DA, Sinn JKH. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006; **4**: CD003741.
54. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy* 2009; **64**: 840–848.
55. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema. *Arch Dermatol* 2007; **143**: 1570–1577.
56. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol* 2009; **161**: 373–383.
57. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 4.2.5 [updated May 2005]. 2005.
58. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
59. AlFaleh KM, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev* 2008; **1**: CD005496.
60. Boyle RJ, Ismail IH, Licciardi PV, Robins-Browne R, Mah LJ, Axelrad C, *et al*. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial (in press). *Allergy* 2011.
61. Dotterud C, Storro O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol* 2010; **163**: 616–623.
62. Hurre A, Laitnen K, Rautava S, Korkeamaki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. *Clin Exp Allergy* 2008; **38**: 1342–1348.
63. Kim JY, Kwon JH, Ahn SH, Lee SI, Han YS, Choi YO, *et al*. Effect of probiotic mix (Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol* 2010; **21**(2 Pt 2): e386–e393.
64. Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. *Pediatrics* 2008; **121**: e850–e856.
65. Niers L, Martin R, Rijkers G, Sengers F, Timmerman H, van Uden N, *et al*. The effects of selected probiotic strains on the development of eczema (the PandA study). *Allergy* 2009; **64**: 1349–1358.
66. Soh SE, Aw M, Gerez I, Chone YS, Rauff M, Ng YP, *et al*. Probiotic supplementation in the first 6 months of life in at risk Asian infants–effects on eczema and atopic sensitization at the age of 1 year. *Clin Exp Allergy* 2009; **39**: 571–578.
67. West CE, Hammarstrom ML, Hernell O. Probiotics during weaning reduce the incidence of eczema. *Pediatr Allergy Immunol* 2009; **20**: 430–437.
68. Wickens K, Black PN, Stanley TV, Mitchell E, Fitzharris P, Tannock GW, *et al*. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2008; **122**: 788–794.
69. Tang ML, Lahtinen SJ, Boyle RJ. Probiotics and prebiotics: clinical effects in allergic disease. *Curr Opin Pediatr* 2010; **22**: 626–634.
70. Muche-Borowski C, Kopp M, Reese I, Sitter H, Werfel T, Schafer T. Allergy prevention. *Dtsch Arztebl Int* 2009; **106**: 625–631.
71. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB, *et al*. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial (in press). *J Allergy Clin Immunol* 2011.

DOI: 10.1002/ebch.827

Appendix

Asthma/wheezing (all ages and risk levels)

Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	4035 (3)	0.95 (0.64, 1.40)	0
Hydrolysed formula versus cow's milk formula (prolonged feeding)	314 (4)	0.57 (0.32, 1.02)	0
Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	96 (1)	0.61 (0.18, 2.04)	—
Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	264 (4)	0.55 (0.29, 1.04)	0
Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	341 (2)	1.72 (0.74, 3.96)	0
Hydrolysed formula versus human milk (early short-term feeding)	90 (1)	0.48 (0.05, 4.41)	—
Hydrolysed formula versus cow's milk formula (early short-term feeding)	77 (1)	3.08 (0.13, 73.26)	—
Soy formula versus cow's milk formula	729 (3)	0.71 (0.26, 1.92)	73
Maternal antigen avoidance versus standard diet	334 (2)	2.22 (0.39, 12.67)	0
Omega-3 fatty acid supplementation versus placebo	1078 (4)	0.81 (0.53, 1.25)	50
Probiotic versus no probiotic	363 (2)	0.82 (0.38, 1.80)	0

Asthma/wheezing subgroup analyses: infants (zero to two years)

Risk level	Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
High risk	Hydrolysed formula versus cow's milk formula (prolonged feeding)	318 (4)	0.58 (0.31, 1.06)	0
	Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	96 (1)	0.61 (0.18, 2.04)	—
	Partially hydrolysed formula versus. cow's milk formula (prolonged feeding)	268 (4)	0.56 (0.29, 1.09)	0
	Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	341 (2)	1.72 (0.74, 3.96)	0
	Soy formula versus cow's milk formula	474 (1)	1.10 (0.86, 1.40)	—
	Maternal antigen avoidance versus standard diet	334 (2)	2.22 (0.39, 12.67)	0
	Omega-3 fatty acid supplementation versus placebo	98 (1)	0.88 (0.51, 1.52)	—
	Probiotic versus no probiotic	363 (2)	0.82 (0.38, 1.80)	0
Not selected for risk	Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	3993 (2)	0.79 (0.48, 1.29)	0

Asthma/wheezing subgroup analyses: children (two to 18 years)

Risk level	Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
High risk	Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	113 (1)	0.54 (0.18, 1.65)	—
	Hydrolysed formula versus cow's milk formula (prolonged feeding)	78 (1)	0.38 (0.08, 1.84)	—
	Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	78 (1)	0.38 (0.08, 1.84)	—
	Soy formula versus cow's milk formula	729 (3)	0.71 (0.26, 1.92)	73
	Omega-3 fatty acid supplementation versus placebo	516 (1)	1.13 (0.82, 1.57)	—
Not selected for risk	Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	439 (1)	1.00 (0.65, 1.54)	—
	Hydrolysed formula versus human milk (early short-term feeding)	90 (1)	0.48 (0.05, 4.41)	—
	Hydrolysed formula versus cow's milk formula (early short-term feeding)	77 (1)	3.08 (0.13, 73.26)	—
	Omega-3 fatty acid supplementation versus placebo	**464 (2)**	**0.48 (0.25, 0.93)** [a]	**0**

[a] Significantly favours omega-3 fatty acid supplementation.
Bold text indicates statistical significance.

DOI: 10.1002/ebch.827

All allergic disease (all ages and risk levels)

Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	113 (1)	0.68 (0.40, 1.17)	—
Hydrolysed formula versus cow's milk formula (prolonged feeding)	**1434 (7)**	**0.75 (0.59, 0.95)**[a]	**38**
Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	747 (2)	0.90 (0.72, 1.11)	0
Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	944 (7)	0.75 (0.57, 1.00)	50
Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	1002 (3)	0.92 (0.77, 1.12)	0
Hydrolysed formula versus human milk (early short-term feeding)	90 (1)	1.43 (0.38, 5.37)	—
Hydrolysed formula versus cow's milk formula (early short-term feeding)	77 (1)	1.37 (0.33, 5.71)	—
Soy formula versus cow's milk formula	283 (2)	0.67 (0.18, 2.46)	95
Maternal antigen avoidance versus standard diet	163 (1)	0.76 (0.42, 1.38)	—
Probiotic versus no probiotic	925 (1)	0.90 (0.75, 1.08)	—

[a] Significantly favours hydrolysed formula (prolonged feeding).
Bold text indicates statistical significance.

All allergic disease subgroup analyses: infants (zero to two years)

Risk level	Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
High risk	**Hydrolysed formula versus cow's milk formula (prolonged feeding)**	**2514 (7)**	**0.76 (0.61, 0.95)**[a]	**20**
	Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	1561 (2)	0.87 (0.68, 1.13)	0
	Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	1482 (7)	0.76 (0.58, 1.00)	38
	Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	1806 (3)	0.93 (0.75, 1.15)	0
	Maternal antigen avoidance versus standard diet	163 (1)	0.76 (0.42, 1.38)	—
	Probiotic versus no probiotic	925 (1)	0.90 (0.75, 1.08)	—

[a] Significantly favours hydrolysed formula (prolonged feeding).
Bold text indicates statistical significance.

All allergic disease subgroup analyses: children (two to 18 years)

Risk level	Comparison	Number of participants (trials)	Risk ratio (95% confidence interval)	I^2 (%)
High risk	Exclusive breastfeeding for at least six months versus introduction of solids at three to six months	113 (1)	0.68 (0.40, 1.17)	—
	Hydrolysed formula versus cow's milk formula (prolonged feeding)	950 (2)	0.67 (0.32, 1.43)	73
	Extensively hydrolysed formula versus cow's milk formula (prolonged feeding)	651 (1)	0.89 (0.71, 1.13)	—
	Partially hydrolysed formula versus cow's milk formula (prolonged feeding)	510 (2)	0.68 (0.31, 1.52)	75
	Extensively hydrolysed formula versus partially hydrolysed formula (prolonged feeding)	661 (1)	0.93 (0.74, 1.18)	—
	Soy formula versus cow's milk formula	283 (2)	0.67 (0.18, 2.46)	95
Not selected for risk	Hydrolysed formula versus human milk (early short-term feeding)	90 (1)	1.43 (0.38, 5.37)	—
	Hydrolysed formula versus cow's milk formula (early short-term feeding)	77 (1)	1.37 (0.33, 5.71)	—

DOI: 10.1002/ebch.827