Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Search Strategies

LIMITERS:
Human

SEARCH STRATEGY:
food hypersensitivity/diagnosis
OR
food hypersensitivity AND (Diagnostic Techniques and Procedures[majr] OR Diagnostic Equipment[majr])
OR
food hypersensitivity AND (test[tiab] OR testing[tiab] OR tests[tiab])
OR
(food*[tiab] AND allerg*[tiab]) AND (diagnosis OR diagnose OR diagnosing OR diagnostic* OR test[tiab] OR testing[tiab] OR tests[tiab])
NOT
case report*

SEARCH STRATEGY:
food hypersensitivity* OR food allerg*
AND
predictive value of tests OR skin tests OR patch tests OR immunologic tests OR radioallergosorbent tests OR in vitro tests
OR
immunoassay OR basophil histamine release assay OR food challenge* OR diagnosis[ti] OR diagnoses[ti] OR diagnostic[ti] OR diagnosing

SEARCH STRATEGY:
acute AND (allergy OR allergies OR allergic) AND (react OR reaction*)
AND
treat OR treated OR treatment* OR therapy OR therapies
NOT
drug allerg* OR drug reaction* OR drug hypersensitiv* OR reaction to drug*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND allergy OR allergies OR allergic OR hypersensitiv*)
AND
anaphylaxis OR anaphylactic
AND
treat OR treated OR treatment* OR therapy OR therapies
NOT
drug allerg* OR drug reaction* OR drug hypersensitiv* OR reaction to drug*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
angioedema*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

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SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
asthma*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
celiac disease OR celiac[tiab]
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR (food allerg*)
AND
colitis

SEARCH STRATEGY:
food hypersensitivity OR (food or foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)
AND
cow* AND milk
AND
colitis OR (blood AND stool*) OR proctocolitis OR (rectal AND bleed*)
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR (food or foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)
AND
dermatitis
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR (food or foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)
AND
dermatitis herpetiformis
NOT
case report* OR case reports[pt]
NOT
animal NOT human
NOT
Results of Search 4f
SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND eosinophilic esophagitis NOT case report* OR case reports[pt] NOT animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND eosinophilic gastroenteritis NOT case report* OR case reports[pt] NOT animal NOT human NOT Results of Search 4h

SEARCH STRATEGY:
food hypersensitivit* OR food allerg* AND exercise OR exercise-induced OR physical activity

SEARCH STRATEGY:
food hypersensitivit* OR food allerg* AND flushing

SEARCH STRATEGY:
(food induced OR food-induced) AND proctocolitis AND syndrome* NOT case report* OR case reports[pt] NOT animal NOT human

SEARCH STRATEGY:
food AND (protein OR proteins) AND enterocolitis AND syndrome* NOT case report* OR case reports[pt] NOT animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND gastrointestinal hypersensitiv* OR vomiting OR colic OR diarrhea NOT case report* OR case reports[pt] NOT animal NOT human
SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND
heiner* OR pulmonary hemisiderosis
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND
inflammatory bowel diseases[mh] OR inflammatory bowel disease*[tiab]
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND
laryngeal edema
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND
milk AND (protein OR proteins) AND infan*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
oral allergy syndrome*

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
rhinitis

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
rhinoconjunctivitis OR conjunctivitis

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*)) AND
urticaria OR hives
NOT
case report* OR case reports[pt]
NOT
animal NOT human
SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
epinephrine
NOT
case report* OR case reports[pt]
NOT
animal NOT human

Cochrane Database of Systematic Reviews
SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(diagnosis or diagnoses or diagnose or diagnostic* or diagnosing or test or tests or testing).mp.

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(treatment or treat or treating or treated or therapy or therapies or therapeutic or manage or management or managing).mp
NOT
Results of Search 1c

Cochrane Database of Abstracts of Reviews of Effects (DARE)
SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(diagnosis or diagnoses or diagnose or diagnostic* or diagnosing or test or tests or testing).mp.

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(treatment or treat or treating or treated or therapy or therapies or therapeutic or manage or management or managing).mp
NOT
Results of Search 1c

Cochrane Central Register of Controlled Trials
SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
AND
(diagnosis or diagnoses or diagnose or diagnostic* or diagnosing or test or tests or testing).mp.

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
AND
(treatment or treat or treating or treated or therapy or therapies or therapeutic or manage or management or managing).mp
NOT
Results of Search 1g

World Allergy Organization Journal – 1988-2009 (February)
SEARCH STRATEGY:
food
References. Bibliography of Studies Assessed for Their Definition of Food Allergy


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eFigure 1. Study Flow Diagram
eFigure 2. QUADAS Quality Scores for Diagnostic Studies

- Were patients representative of those who will receive the test?
- Were selection criteria clearly described?
- Is the reference standard likely to correctly classify the target condition?
- Is the time period between reference standard and index test short enough?
- Did the whole sample receive verification?
- Did patients receive the same reference standard?
- Was the reference standard independent of the index test?
- Was the execution of the index test described sufficiently?
- Was the execution of the reference standard described sufficiently?
- Were the index test results interpreted independent of the reference standard?
- Were the reference standard results interpreted independent of the index test?
- Were withdrawals from the study explained?
### eTable 1. Studies of Management of Food Allergies

<table>
<thead>
<tr>
<th>Author</th>
<th>Inclusion/Exclusion</th>
<th>Intervention</th>
<th>Control</th>
<th>Food(s) Evaluated</th>
<th>Outcomes</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td><strong>Elimination diets</strong></td>
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<tr>
<td>Agata, 1993³³</td>
<td>Inclusion: clinical history of atopic dermatitis and milk/egg allergy</td>
<td>Cow’s milk: n=16 Hen’s egg: n=27 Elimination diet</td>
<td>Cow’s milk: n=5 Hen’s egg: n=6 No elimination diet</td>
<td></td>
<td>After 3 month; Cow’s milk: 15/16 showed improvement in their AD with elimination diet; compared with 0/5 not on an elimination diet. Hen’s egg: 27/27 showed improvement in AD with an elimination diet; compared with 0/6 not on an elimination diet.</td>
<td>Poor</td>
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<tr>
<td><strong>Immunotherapy</strong></td>
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<tr>
<td>Patriarca, 2007³⁹</td>
<td>Consecutive children affected by food allergy (defined by clinical history, skin prick tests, serum total and specific IgE, and DBPCFC)</td>
<td>Cow’s milk: n=18 Hen’s egg: n=17 Fish: n=9 Desensitization per a protocol to the food(s) to which each person was allergic--increasing in dose every 3 days. Patients were then asked to eat the allergenic food at least 2x week</td>
<td>n=10 Continued elimination diet</td>
<td></td>
<td>Cow’s milk: 12/18 patients that underwent desensitization compared with 0/10 control patients had a negative DBPCFC. Hen’s egg: 12/17 patients that underwent desensitization compared with 0/10 control patients had a negative DBPCFC. Fish: 9/9 patients that underwent desensitization compared with 0/10 control patients had a negative DBPCFC.</td>
<td>Poor</td>
</tr>
<tr>
<td>Staden, 2007³⁴</td>
<td>Inclusion: IgE-mediated food allergy to either cow’s milk or hen’s egg as confirmed by DBPCFC Exclusions: severe atopic dermatitis with SCORAD &gt;75</td>
<td>n=25 Assigned to specific oral tolerance induction with both an induction and maintenance phase. Patients then underwent an elimination diet for 2 months prior to follow-up food challenge</td>
<td>n=20 Elimination diet</td>
<td></td>
<td>Tolerance was achieved more often in the group that received oral tolerance induction (16/25) than in the group that adhered to an elimination diet (7/20) p=0.05.</td>
<td>Good</td>
</tr>
<tr>
<td>Morisset, 2007³⁵</td>
<td>Inclusion: Children with cow’s milk allergy or hen’s egg allergy as established on the basis of 1. skin prick test OR specific IgE AND 2. confirmed by either positive oral/labial food challenge OR complete recovery from symptoms after 3 weeks of food avoidance.</td>
<td>Cow’s milk: n=28 Hen’s egg: n=51 Oral desensitization with whole pasteurized milk for those with cow’s milk allergy, in weekly increasing doses. Oral desensitization with hard-boiled eggs for those with hen’s egg allergy, in weekly increasing doses</td>
<td>Cow’s milk: n=32 Hen’s egg: n=39 Continued avoidance of either milk or egg</td>
<td></td>
<td>Cow’s milk: Significant decrease in the size of the SPT wheal (p&lt;0.002) and a significant improvement in DBPCFC (3/27 vs 12/30 p&lt;0.025) Hen’s egg: Statistically significant decrease in the size of the SPT wheal (p&lt;0.005) and a decrease in slgE. Significant improvement in DBPCFC (15/49 vs 17/35; p&lt;0.1)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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<th>Author</th>
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<tbody>
<tr>
<td>Skripak, 2008</td>
<td>Inclusion: children aged 6-21 from pediatric allergy clinics with positive SPT to milk extract, milk IgE &gt;0.35 kU/L with a positive milk challenge result to 2.5 g or less of milk protein. Exclusion: history of anaphylaxis requiring hospitalization, history of intubation related to asthma, or a current diagnosis of severe, persistent asthma.</td>
<td>Immunotherapy dose schedule that was initiated in the clinic and then patient continued with maximum tolerated dose at home for 7-14 days. The patient returned to the clinic to get a dose increase. Once a dose of 500 mg (=15mL of milk) was achieved, patient continued on that dose for 13 weeks.</td>
<td>n=7 Placebo</td>
<td>Milk dose threshold and cow’s milk-specific IgG levels were higher in the group receiving oral immunotherapy (p=0.002). There was no statistically significant change in cow-milk-specific IgE.</td>
<td>Good</td>
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<td>Nelson, 1997</td>
<td>Adults with a history of immediate hypersensitivity reactions to peanuts</td>
<td>Injections of peanut extract--a maintenance level of tolerance was first achieved by a rush protocol, then maintained with weekly injections for at least a year.</td>
<td>n=6 No treatment</td>
<td>Decreased peanut sensitivity at one month (p=0.0002) but no effect on SPT or peanut-sIgE as compared to patients who did not receive subcutaneous injections.</td>
<td>Poor</td>
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<tr>
<td>Enrique, 2005</td>
<td>Inclusion: positive DBPCFC with hazelnuts. Exclusion: pregnancy, uncontrolled asthma, systemic steroids, B-blockers, antihistamines, antidepressants, systemic disease not compatible with the treatment</td>
<td>Biologically standardized hazelnut extract given in increasing concentrations for 5 days</td>
<td>n=11 Saline solution in vials with exactly the same appearance, color, and taste but without allergens</td>
<td>Mean hazelnut quantity that provoked symptoms increased in the group receiving hazelnut extract but not in the placebo group (p=0.02). An an increase in hazelnut-specific IgG4 (p&lt;0.05) but no difference in the hazelnut-specific IgE between the groups.</td>
<td>Good</td>
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<tr>
<td>Bucher, 2004</td>
<td>Inclusion: oral allergy syndrome induced by apple or hazelnut with a positive SPT to birch pollen AND hazelnut or apple</td>
<td>Subcutaneous immunotherapy with tree pollen extract</td>
<td>n=12 Did not receive tree extract immunotherapy</td>
<td>Improvement of oral allergy syndrome was statistically significant (p&lt;0.05) with 10/15 patients receiving subcutaneous immunotherapy showing improvement (compared with only 2/12 control patients). sIgE to apple was also measured and the difference was found to be NS.</td>
<td>Poor</td>
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<tr>
<td>Klemola, 2002&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Infants with IgE or non-IgE cow's milk allergy diagnosed by DBPCFC or a history of anaphylaxis with cow's milk and presence of sIgE</td>
<td>n=80 mean age: 7.1 years. Fed soy milk</td>
<td>n=90 mean age: 6.9 years Fed eHF</td>
<td></td>
<td>Incidence of adverse reactions confirmed by DBPCFC was lower for both the soy formula (8 infants: 10%, 95% CI 4.4-18.8%) and for the eHF (2 infants: 2.2%; 95% CI 0.3-7.8) Statistically significantly greater in the soy formula group (relative risk =4.50, p =0.03).</td>
<td>Fair</td>
</tr>
<tr>
<td>Niggemann, 2008&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Infants with cow's milk allergy</td>
<td>n=34 Fed eHF with lactose</td>
<td>n=32 Fed amino acid formula</td>
<td></td>
<td>No difference in tolerance or growth parameters.</td>
<td>Fair</td>
</tr>
<tr>
<td>Garzi, 2002&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Children with GERD thought to be related to cow's milk</td>
<td>n=10 eHF</td>
<td>n=10 CMF</td>
<td></td>
<td>Unable to statistically evaluate the gastric emptying time or GERD symptoms.</td>
<td>Poor</td>
</tr>
<tr>
<td>Savino, 2005&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Infants with atopic dermatitis and cow's milk allergy</td>
<td>rHF: n=15 soy: n=17 eHF-C: n=26</td>
<td>n=30 Free diet</td>
<td></td>
<td>No significant differences in the z-score weight for age.</td>
<td>Fair</td>
</tr>
<tr>
<td>Jirapinyo, 2007&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Infants and children (aged 2-24 months) with a diagnosis of cow's milk allergy</td>
<td>n=20 14 days of chicken meat formula</td>
<td>n=18 14 days of soy formula</td>
<td></td>
<td>12/18 children who received the soy formula were intolerant to it compared to 4/20 children who received the chicken-meat based formula (p=0.009).</td>
<td>Fair</td>
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<tr>
<td>Vita, 2007&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Children with atopic dermatitis from cow's milk</td>
<td>n=14 Ass’s milk</td>
<td>n=14 Goat’s milk</td>
<td></td>
<td>Ass milk significantly improved both the SCORAD index and the visual analog scale (p&lt;0.03) whereas goat milk had no effect.</td>
<td>Fair</td>
</tr>
<tr>
<td>Iacono, 1998&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Children with chronic constipation from cow's milk allergy. Cross-over study</td>
<td>n=65 Soy milk</td>
<td>n=65 Cow’s milk</td>
<td></td>
<td>Soy milk significantly increased the number of bowel movements (p&lt;0.001).</td>
<td>Good</td>
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<tr>
<td>Salpietra, 2005&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Infants with cow’s milk allergy</td>
<td>Almond milk: n=26 Soy formula: n=13 Protein formula: n=13</td>
<td>n=13 &quot;Formula fed&quot; not otherwise specified</td>
<td></td>
<td>Reduced symptoms (e.g., vomiting, diarrhea, wheezing, eczema) among children taken off cow’s milk but no difference in those given almond milk compared to soy-based formula or hydrolyzed formula.</td>
<td>Fair</td>
</tr>
<tr>
<td>Author</td>
<td>Inclusion/Exclusion</td>
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<td>Quality</td>
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<td><strong>Diet in breastfeeding women</strong></td>
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<td>Hill, 2005&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Inclusion: exclusively breast fed infants &lt;6 weeks with colic, term infants, normal singleton pregnancy, uneventful perinatal history, no perinatal morbidity other than distress. Exclusion: mothers on strict vegan diets</td>
<td>Maternal diet that was low allergen, excluding dairy products, soy, wheat, eggs, peanuts, tree nuts, and fish</td>
<td>n=47</td>
<td>n=43</td>
<td>Regular diet including 7 day supply of cow and soy powder, 1 serving of peanuts, 1 serving of wheat, and 1 chocolate muesli bar/day</td>
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<tr>
<td><strong>Medical/Pharmacologic therapies</strong></td>
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<tr>
<td>Cavagni, 1989&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Children with a food allergy manifesting as atopic dermatitis</td>
<td>Food to which a positive prick test was found was excluded from the diet for 90 days. During this period, treatment group received 120 mg/day of thymomodulin</td>
<td>n=10</td>
<td>n=9</td>
<td>Same as experimental group but received placebo rather than thymomodulin</td>
<td>•</td>
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<tr>
<td>Businco, 1990&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Cross-over trial in which children underwent a washout elimination diet followed by on-going elimination diet with either placebo or sodium cromoglycate. Subjects then crossed into the other arm</td>
<td>Sodium cromoglycate</td>
<td>n=31</td>
<td>n=31</td>
<td>Placebo</td>
<td>•</td>
</tr>
<tr>
<td>Author</td>
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<tr>
<td>Burks, 1988&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Inclusion: AD as defined by Hanifin and Rajka, positive SPT, strict egg-avoidance diet for one year, antihistamines stopped one week before trial, and beta-agonists were stopped 12 hours before trial.</td>
<td>n=10 Treated for a week with either cromolyn or placebo and then evaluated. Patients then had a washout period of three to five weeks and were crossed over to the other arm for a week and again evaluated.</td>
<td>n=10 Same</td>
<td>●</td>
<td>No statistically significant difference in the symptom score for AD or in the response to a DBPCFC.</td>
<td>Fair</td>
</tr>
<tr>
<td>Leung, 2003&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Inclusion: Serum total IgE between 30 and 1000 IU/mL, good health, body weight within 20% of ideal, positive SPT to peanut and negative SPT to tuna oil</td>
<td>150-mg n=19; 300-mg n=19; 450-mg n=21 3 groups receiving different doses of TNX-901 (150 mg, 300 mg, 450 mg), a humanized IgG1 monoclonal antibody against IgE</td>
<td>n=23 Placebo</td>
<td>●</td>
<td>A 450-mg dose of TNX-901, a humanized IgG1 monoclonal antibody, increased the threshold of sensitivity to peanut on oral food challenge from a level equal to one half a peanut to almost nine peanuts.</td>
<td>Good</td>
</tr>
<tr>
<td>Bindslev-Jensen, 1991&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Inclusion: case history of immediate local symptoms (itching and swelling of mouth/throat) Exclusion: anamnesic severe reaction after intake of hazelnuts</td>
<td>n=15 Aztemizole 10 mg each morning for 14 days followed by 2 open oral provocations</td>
<td>n=15 Placebo</td>
<td>●</td>
<td>Symptom severity to the oral provocation test was statistically significantly lower in the group that got aztemizole than in the placebo group (p=0.004).</td>
<td>Fair</td>
</tr>
<tr>
<td>Author</td>
<td>Inclusion/Exclusion</td>
<td>Intervention</td>
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<tr>
<td>Szajewska, 2007</td>
<td>Inclusion: rectal bleeding diagnosed as the presence of blood-streaked normal-to-soft stools, exclusive breastfeeding, age &lt; 6 months. Exclusion: infectious origin of rectal bleeding, necrotizing enterocolitis, and coagulopathies</td>
<td>n=11 Mothers eliminated cow milk from their diet and infants received lactobacillus fermentum GG</td>
<td>n=15 Mothers eliminated cow milk from their diet and infants received placebo</td>
<td>NS effect on reducing the number of days of rectal bleeding.</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Viljane n, 2005</td>
<td>Inclusion: infants under 12 months upon entering the study, symptoms suggestive of cow’s milk allergy, obligatory atopic eczema/dermatitis Exclusion: No probiotic preparations used longer than 1 week and within 6 weeks of entering the study</td>
<td>Lactobacillus alone: n=44 Mixture: n=44 Elimination diet and skin treatment with 4 weeks of lactobacillus or a mixture of lactobacillus and other probiotics</td>
<td>n=32 Elimination diet and skin treatment with 4 weeks of placebo</td>
<td>There was no statistically significant change in the SCORAD scores.</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Ewan, 2001</td>
<td>Inclusion: patients with peanut and nut allergy</td>
<td>n=567 Advice on avoidance and medications to use in case of an accidental ingestion of peanuts; medications also provided</td>
<td>N/A</td>
<td>88/567 (15%) patients had a follow-up reaction of reduced severity and only 3/567 (0.5%) patients, had a severe follow-up reaction, compared with 12% initially.</td>
<td>Poor</td>
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</table>

RCT=randomized control trial; IgE=immunoglobulin E; sIgE=specific immunoglobulin E; HF=hydrolyzed formula; eHF=extensively hydrolyzed formula; eHF-W=extensively hydrolyzed whey formula; eHF-C=extensively hydrolyzed casein formula; pHF=partially hydrolyzed formula; pHF-W=partially hydrolyzed whey; pHF-C=partially hydrolyzed casein; CMF=cow’s milk formula; rHF=rice hydrolysate formula; AD=atopic dermatitis; SCORAD=scoring atopic dermatitis; CMA= cow’s milk allergy; mo=month(s); wk=week(s); yr=year(s); GERD=gastroesophageal reflux disease; DBPCFC=double blind placebo controlled food challenge; RR=relative risk; CI=confidence intervals; N/A=not applicable; SPT=skin prick test; CM=cow’s milk; HE=hen’s egg; P=peanut/tree nut; F=shellfish/fish; AAP=American Association of Pediatrics
<table>
<thead>
<tr>
<th>Author</th>
<th>Inclusion/Exclusion</th>
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<tbody>
<tr>
<td><strong>Breastfeeding and delayed introduction of solid foods</strong></td>
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<tr>
<td>Halmerbauer, 2002&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Inclusion: infants with allergic disease in one or both parents, confirmed by allergy testing. Exclusion: birth weight less than 2500 grams; admission to NICU for more than 7 days</td>
<td>n=349 Exclusive breastfeeding for as long as possible and at least until 3 months of age; Introduction of solids and soy milk delayed until 6 months; hypoallergenic formula used if supplementation required prior to 6 months; Cow’s milk, hen’s egg and fish after 12 months; peanut or tree nuts after 3 years; Environmental measures for anti-dust-mite procedures; all beds in child's room had special dust-mite protection covers</td>
<td>n=347 Same recommendations made as those to intervention group; no protective mattress cover provided</td>
<td>Significantly reduced risk of parent reported food intolerance (vomiting, prolonged crying, diarrhea, or swollen lips after eating)</td>
<td>Fair</td>
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<tr>
<td>Kajosaari, 1994&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Inclusion: infants of atopic parents</td>
<td>n=51 Exclusive breastfeeding until 6 months of age; no introduction of solid foods until 6 months of age</td>
<td>n=62 Exclusive breastfeeding until 3 months of age at which time solid feeding was started</td>
<td>Higher incidence of atopy in the control group that did not reach conventional levels of statistical significance (p=0.15), but no differences in rates of asthma, atopic eczema, or fresh fruit allergy.</td>
<td>Poor</td>
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<td><strong>Maternal diet during pregnancy or lactation</strong></td>
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<td>Kramer, 2006&lt;sup&gt;58&lt;/sup&gt; (systematic review)</td>
<td>RCTs or quasi-RCTs comparing diets of different levels of antigen avoidance. Cochrane Pregnancy and Childbirth Group Trial register; Up to March 2006</td>
<td>4 studies with 334 women Mothers prescribed a diet to either exclude or reduce potentially allergenic foods: cow milk, egg, peanuts, fish, chocolate during pregnancy or lactation</td>
<td>No significant difference in the incidence positive skin prick tests to cow’s milk (RR 0.86; 95% CI 0.16-4.59) or hen’s egg (RR 0.95; 95% CI 0.52-1.74) during the first 18 months of life in infants whose mothers avoided dietary antigens during pregnancy.</td>
<td>Good</td>
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<td>Hattevig, 1989&lt;sup&gt;91&lt;/sup&gt; and Sigurs, 1992&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Intervention: Inclusion: children included if they had double heredity (both parents, one parent and one sibling, or two siblings) or if they had single heredity and cord blood IgE level &gt;= 0.9 kU/L; nonsmoking families with no indoor pets.</td>
<td>n=65 Lactating mothers diet up to 3 months post-partum to be free from hen’s egg, cow’s milk and fish product. After 3 months all returned to normal diet. Infants: cow’s milk after 6 months and fish after 9 months; during first 6 months breastfeeding or hydrolyzed casein formula</td>
<td>n=50 Mothers: no restriction on diet. Infants: same as intervention group</td>
<td>No significant differences in adverse reactions to cow’s milk or hen’s egg or in positive skin prick tests or positive sIgE tests at 18 months or 4 years of age.</td>
<td>Poor</td>
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<td><strong>Exclusive breastfeeding</strong></td>
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<td>Schoetzau, 2002⁹⁵</td>
<td>Inclusion: Infants with family history of allergy in the German Nutritional Intervention Study cohort study.</td>
<td>n=865 Infants were exclusively breastfed for at least 4 months</td>
<td>n=256 Partially or exclusively received cow milk formula</td>
<td>Significantly lower risk of atopic dermatitis at one year of age in infants who were exclusively breastfed (9.5%) compared to infants who were not (14.8%) p=0.015.</td>
<td>Fair</td>
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<td>Laubereau, 2004¹¹⁰</td>
<td>Inclusion: infants with family history of atopy</td>
<td>Exclusive breast feeding intervention: n=900 Exclusive breast feeding non-intervention: n=1131 Mothers encouraged to breastfeed for at least 4 months; if this was not possible then they were to use one of four hydrolyzed formulas; delayed introduction of solids until 4 months and potentially allergic food to be delayed until 1st year</td>
<td>Non-exclusive breastfeeding intervention: n=684 Non-exclusive breastfeeding non-intervention: n=1188 Did not receive any dietary recommendations</td>
<td>Exclusive breast-feeding was not associated with higher risk for atopic dermatitis either in the entire cohort (OR, 0.95; 95% CI, 0.79-1.14) or if stratified by family history of atopic dermatitis. In the intervention subgroup, but not in the non-intervention subgroup, exclusive breast-feeding showed a significant protective effect on atopic dermatitis if compared with conventional cow’s milk formula (OR, 0.64; 95% CI, 0.45-0.90).</td>
<td>Fair</td>
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<td>Filipiak, 2007⁹³</td>
<td>Inclusion: Infants with family history of allergy in the German Nutritional Intervention Study cohort study.</td>
<td>n=1939 Specific recommendations to mothers for breastfeeding, use of hydrolyzed formula, and delayed introduction of solids</td>
<td>n=2814 No recommendations</td>
<td>No evidence to support a protective effect of breastfeeding for eczema.</td>
<td>Poor</td>
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<td><strong>Special diets in infants</strong></td>
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<td>Osborn, 2006⁶⁶ (systematic review)</td>
<td>RCTs or quasi-RCTs with &gt; 80% follow up Medline (1966-March 2006; EMBASE (1980-March 2006); CINAHL (1982-March 2006); Cochrane Central (up to March 2006)</td>
<td>7studies included use of any HF</td>
<td></td>
<td>Prolonged feeding with HF vs. CMF in infants at high risk, significant decrease in infant allergies (RR: 0.79 95% CI 0.66-0.94), but no difference in the incidence of childhood allergy or infant or childhood eczema, asthma, rhinitis and food allergy. Similar for pHF. No significant difference in outcomes for eHF vs. CMF. Significant decrease in food allergy for eHF vs pHF (RR 0.43; 95% CI 0.19-0.99). Significant decrease in incidence of infant eczema (0.71; 95% CI 0.51-0.97) for eHF-C vs CMF</td>
<td>Good</td>
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<td>Osborn, 2006&lt;sup&gt;59&lt;/sup&gt; (systematic review)</td>
<td>RCTs or quasi-RCTs with &gt; 80% follow up; cross-over trials excluded Medline (1966-March 2006; EMBASE (1980-March 2006); CINAHL (1982-March 2006); Cochrane Central (up to March 2006)</td>
<td>3 studies included use of an adapted soy formula</td>
<td></td>
<td>No significant differences in incidence of childhood allergies, infant or childhood asthma, infant or childhood eczema, or infant or childhood rhinitis.</td>
<td>Good</td>
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<td>Hays, 2005&lt;sup&gt;61&lt;/sup&gt; (systematic review)</td>
<td>Inclusion: controlled trials to assess the effect of hydrolyzed formulas in preventing allergies when compared with breastfeeding, cow’s milk formula, or soy formula and the difference between eHF and pHF</td>
<td>9 studies on eHF-C and 11 studies on pHF (10 pHF-W and 1 pHF-C).</td>
<td></td>
<td>Given heterogeneity, unable to pool data, but narrative conclusion that the data support a protective effect but short of the AAP criteria for allergy prevention.</td>
<td>Fair</td>
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<td>Arslanoglu, 2008&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Inclusion: infants with a family history of atopy</td>
<td>n=66 Hypoallergenic milk with IMMUNOFORTIS</td>
<td>n=68 Hypoallergenic milk</td>
<td>The cumulative incidences of AD, recurrent wheezing, and allergic urticaria were lower in the treatment group than the control group (13.6 vs 27.9 percent, 7.6 vs 20.6 percent, 1.5 vs 10.3 percent respectively, p&lt;0.05).</td>
<td>Good</td>
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<td>Szajewska, 2004&lt;sup&gt;99&lt;/sup&gt;</td>
<td>Inclusion: preterm infants</td>
<td>eHF: n=20 pHF: n=22</td>
<td>n=26 Standard preterm formula</td>
<td>No difference in the incidence of allergic diseases.</td>
<td>Good</td>
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<td>Von Berg, 2007 and 2008&lt;sup&gt;96, 97&lt;/sup&gt;</td>
<td>Inclusion: infants with at least 1 parent or sibling with a history of allergic disease, less than 2 weeks old, and without any history of formula supplementation</td>
<td>pHF-W: n=557 eHF-W: n=559 eHF-C: n=580</td>
<td>n=556 Received CMF</td>
<td>Children fed pHF-W and eHF-C were less likely to have any allergy diagnosis vs. children fed CMF (47.1 percent, 46.1 percent, vs 56 percent). No difference between eHF-W and CMF</td>
<td>Good</td>
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<td>De Jong, 1998&lt;sup&gt;107&lt;/sup&gt; and 2002&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Newborns</td>
<td>n=758 Brief exposure to cow’s milk protein in the first days of life</td>
<td>n=775 Placebo in the first days of life</td>
<td>Up to 5 years later, no difference in specific IgE, atopic disease, or wheezing.</td>
<td>Good</td>
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<td>Odelram, 1996&lt;sup&gt;98&lt;/sup&gt;</td>
<td>Inclusion: at least 2 atopic family members or one atopic parent, total cord blood IgE was &gt;0.5 kU/L. Exclusion: gestational age below 37 weeks, complicated delivery, neonatal illness, severe birth defects, documented or expected noncompliance with diet prescriptions</td>
<td>Group 1 (eHF-W): 19 males; 13 females. Group 2 (CMF): 23 males; 16 females. Lactating mothers and infants were on elimination diets for cow milk, egg, and fish and received formula.</td>
<td>Exclusively fed breast milk for &gt; 9 months: 6 males; 14 females Lactating mothers and infants were on elimination diets for cow milk, egg, and fish</td>
<td>No statistically significant difference in positive SPT or in serum IgE at 18 months.</td>
<td>Fair</td>
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<td>Lindfors, 1992&lt;sup&gt;108&lt;/sup&gt;</td>
<td>Term but low birth weight</td>
<td>n=109 CMF in the first few days of life prior to full breastfeeding</td>
<td>n=98 Breast milk only</td>
<td>9/95 (9.5%) children who had received cow’s milk and 9/88 (10.2%) children who had been exclusively breast fed had evidence of obvious allergic disease at age 4-6 years.</td>
<td>Fair</td>
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<td>Bardare, 1993&lt;sup&gt;94&lt;/sup&gt;</td>
<td>Inclusion: newborns with family risk of atopy; family risk defined as history of atopy in either parent or siblings who had been clinically diagnosed with allergy (respiratory, atopic eczema, urticaria, GI complaints qualified as allergies); cord blood IgE levels &gt;= 1 IU/mL</td>
<td>n=158 Infants: soy formula supplementation if required; gluten after 8th month; cow milk and dairy products after 10th month; lamb, turkey rabbit, pear, pineapple allowed before 1 year; avoidance of tobacco smoke and animal dander recommended; Mother during breastfeeding: no more than 200 mL of milk and only one egg per week; completely avoid tomato, fish, shellfish, nuts and other foods to which the mother was allergic</td>
<td>n=218 No diet prescribed; parents informed of infant's atopy risk</td>
<td>Lower incidence of atopy in the first year of life in infants with parents that were compliant with the prescribed diet 13.3% than infants with parents that were offered no dietary recommendations 28.9%</td>
<td>Poor</td>
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<td>Probiotics</td>
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<td>Huurre, 2008&lt;sup&gt;102&lt;/sup&gt;</td>
<td>Inclusion: enrolled in the nutrition modulation by dietary counseling for allergic families; no chronic or metabolic disease in the mother before or during early pregnancy, and completed follow-up and SPT of the infant at age 1 year.</td>
<td>n=72 Dietary counseling, breastfeeding, L rhamnosus and B lactis from first trimester of pregnancy to the end of exclusive breastfeeding.</td>
<td>n=68 Placebo</td>
<td>No difference in positive reactions to SPT at one year between the children of women who received probiotics (29 percent) and those who did not (31 percent; OR: 0.92, 95% CI 0.45-1.90, p=0.825).</td>
<td>Good</td>
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<td>Rautava, 2002&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Inclusion: pregnant women from atopic families; included breast-feeding women and the maternal use of probiotics until age 3 months</td>
<td>n=30 Starting 4 weeks before term and continuing for 3 months post partum (with breastfeeding), <em>L</em> rhamnosus probiotics given to mother and then to neonate</td>
<td>n=32 Placebo</td>
<td>4/27 children of the women who received probiotics developed chronic relapsing atopic eczema compared with 14/30 whose mothers received placebo (RR 0.32, 95% CI 0.12-0.85, p=0.0098).</td>
<td>Good</td>
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<td>Kuitunen, 2009&lt;sup&gt;103&lt;/sup&gt; &amp; Kukkonen, 2007&lt;sup&gt;104&lt;/sup&gt;</td>
<td>Inclusion: pregnant mothers carrying children at increased risk for allergy. Exclusion: Infants born before 37 weeks, with major malformations, and B-twins</td>
<td>n=506 Starting at week 35 gestation, mothers took 1 capsule of <em>Lactobacillus</em>, <em>Bifidobacterium</em> and <em>propionibacterium</em> species bid. The newborn infants received 1 opened capsule of the same mixed with 20 drops of sugar containing galacto-oligosaccharides once daily for the first 6 months of life.</td>
<td>n=512 Identical appearing capsules of cellulose</td>
<td>No significant differences in the primary end points of allergic and IgE-associated allergic disease or frequencies of eczema, asthma, allergic rhinitis, or atopic sensitization in the probiotic and placebo arms at 5 years.</td>
<td>Good</td>
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<td>Abrahamsson, 2007&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Families with allergic disease were recruited at antenatal clinics; diagnosis made by family history.</td>
<td>n=95 Mothers started taking <em>L</em> reuteri 4 weeks before term and continued daily after delivery. After birth, baby continued same preparation for 12 months.</td>
<td>n=93 Mothers started taking placebo 4 weeks before term and continued daily after delivery. After birth, baby continued same preparation for 12 months.</td>
<td>Cumulative incidence of eczema was not different between the treatment (36%) and placebo groups (34%), and no difference in the cumulative incidence of wheeze at 24 months. IgE-mediated eczema was lower in the probiotics group (8 percent versus 20 percent; p=0.02) as was the circulating IgE to egg white—although not to other food allergens.</td>
<td>Good</td>
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NICU=neonatal intensive care unit; RCT=randomized control trial; IgE=immunoglobulin E; sIgE=specific immunoglobulin E; HF=hydrolyzed formula; eHF=extensively hydrolyzed formula; eHF-W=extensively hydrolyzed whey formula; eHF-C=extensively hydrolyzed casein formula; pHF=partially hydrolyzed formula; pHF-W=partially hydrolyzed whey; pHF-C=partially hydrolyzed casein; CMF=cow's milk formula; RR=relative risk; CI=confidence intervals; SPT=skin prick test AAP=American Association of Pediatrics; dL=deciliters